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Carole Kenner • Leslie B. Altimier • Marina V. Boykova
EDITORS

SIXTH EDITION

COMPREHENSIVE NEONATAL NURSING CARE

Comprehensive Neonatal Nursing Care

Carole Kenner, PhD, RN, FAAN, FNAP, ANEF, is the Carol Kuser Loser Dean/Professor of the School of Nursing, Health, and Exercise Science at The College of New Jersey. Dr. Kenner received a bachelor's of science in nursing from the University of Cincinnati and her master's and doctorate in nursing from Indiana University. She specialized in neonatal/perinatal nursing for her master's and obtained a minor in higher education for her doctorate. She has authored more than 100 journal articles and 30 textbooks.

Her career is dedicated to nursing education and to the health of neonates and their families, as well as educational and professional development of healthcare practices in neonatology. Her dedication includes providing a healthcare standard for educating neonatal nurses nationally and internationally. Her passion led her to begin the journal *Newborn and Infant Nursing Reviews*, in which she served as editor and then associate editor. She worked with the National Coalition on Health Professional Education in Genetics (NCHPEG) and the American Nurses Association to develop genetic competencies. She helped develop the End-of-Life Nursing Education Consortium (ELNEC) Neonatal/Pediatric modules. She served as the co-chair of the Oklahoma Attorney General's Task Force on End of Life/Palliative Care. She also helped develop program recommendations for perinatal/neonatal palliative care as part of a family-centered/developmental care project sponsored by the National Perinatal Association. She serves on the Consensus Committee of Neonatal Intensive Care Design Standards, which sets recommendations for Neonatal Intensive Care Unit designs, and serves on the March of Dimes Nursing Advisory Committee. She is a fellow of the American Academy of Nursing (FAAN), a fellow in the National Academies of Practice, a fellow in the Academy of Nursing Education, past president of the National Association of Neonatal Nurses (NANN), and founding president of the Council of International Neonatal Nurses (COINN), the first international organization representing neonatal nursing-setting standards globally. She is the 2011 recipient of the Audrey Hepburn Award for Contributions to the Health and Welfare of Children Internationally.

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I wish to first express my appreciation, love, and support for my dad, who died in 2017 at the age of 105½. He always got excited when a new edition published.
—Carole

I would like to thank my children, Jen, Julie, and Kevin, for their love, support, and encouragement for me as a mom and as a professional.
—Leslie

For my mom, whose love and support were endless.
—Marina

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—Carole Kenner, Leslie Altimier, and Marina Boykova

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Foreword

Comprehensive Neonatal Nursing Care has been the go-to resource for evidence-based and practical guidance for novice and expert neonatal nurses in classroom and clinical settings since 1993. As we have come to expect and rely upon, the new *sixth edition* includes the latest information on neonatal embryology, physiology, medical and surgical management, psychosocial care, emerging infections, neuroprotection, pain control, care of the late preterm infant, and much more. The textbook is organized with a focus on integrative management of the newborn and family. There is extensive use of research findings in each of the chapters to provide evidence to support practice strategies and clinical decision-making. Complete references are found at the end of each chapter.

In the new *sixth edition*, the chapters have been thoroughly updated and refreshed with the latest research and practice tips, written by authors who are recognized experts in their fields. New features include callouts highlighting parent perspectives, quality and safety practice points, and emergency alerts. There are new chapters on trauma-informed care, neonatal abstinence, and support for families. Uniquely among neonatal textbooks, the *sixth edition* of *Comprehensive Neonatal Nursing Care* includes a focus on the neonatal care ecosystem, with chapters on emerging trends in research and care delivery, genetics and genomics, and competency-based education and support for neonatal unit managers and directors.

In today's world, neonatal nurses are faced with the constant threat of information overload and ever-present concerns about the accuracy and relevance of what appears in print, online, and in videos, blogs, podcasts, or instant messages. It is therefore reassuring—and indeed essential—to have the well-written, accessible, thoroughly researched and accurate *Comprehensive Neonatal Nursing Care* as our constant and trustworthy companion as we strive to provide high-quality care to all newborns and their families. The editors and authors are to be congratulated for maintaining such a high standard of excellence and practical application. Your dedication enables neonatal nurses everywhere to provide essential care to the more than 30 million sick and premature newborns and their families who depend on nurses to survive and thrive.

Thank you!

Linda S. Franck, PhD, RN, FRCPCH, FAAN
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Preface

One of the most complex issues in healthcare is the care of sick or premature infants and those with multiple, severe congenital anomalies. Despite advanced technology and knowledge, preterm delivery continues to be a significant problem in the United States. Maternal risk factors have changed over the past decade. For example, more women with congenital heart anomalies and chronic illnesses, such as diabetes or sickle cell anemia, are giving birth to infants with consequent health problems. The rise of in vitro fertilization has resulted in increased multiple births and prematurity. Many infants in neonatal intensive care units (NICUs) have been exposed to substances or are born to mothers with other risk factors such as delayed childbearing or childhood cancers.

The care of these at-risk infants requires the use of more and more complex technology. Surfactant administration, nitric oxide administration, high-frequency jet ventilators, neurally adjusted ventilatory assist (NAVA; Stein & Firestone, 2014), and new hybrid ventilators providing high-frequency and conventional modes of ventilation are being used in Europe and are likely to be brought to the United States for Food and Drug Administration (FDA) approval. New technologies now can provide continuous, noninvasive monitoring of endotracheal tube position and obstruction (Hütten et al., 2015). Servo-controlled oxygen administration, which leads to greater compliance with targeted oxygen saturation ranges, is being developed (Claure & Bancalari, 2015). Near-infrared spectroscopy (NIRS), amplitude-integrated EEGs (aEEGs), dialysis, organ transplantation, and other extraordinary measures are becoming commonplace. Better integration of technologies (both electronic medical records [EMRs] and medical devices) will be the basis for decision support and predictive analytics. However, in the midst of these high-tech interventions, neuroprotective developmentally supportive care interventions such as olfactory and gustatory support, using visible rather than audible alarms, music therapy, cycling lights, using more physiologically and developmentally appropriate positioning, and skin-to-skin contact are being recognized as evidence-based neuroprotective interventions, due to increasing evidence regarding the importance of maintaining a developmentally supportive NICU environment for improved long-term infant/child and family outcomes. Some consequences of prematurity are caused by early parent–infant separation and a lack of parents' participation in the care of their infant during traditional neonatal intensive care. The family is an essential partner in decision-making and care for their infant, and family-centered care is being expanded to family-integrated care, a paradigm shift from nurse caring to nurse coaching for parents providing the care.

Providers of neonatal care need up-to-date accurate and comprehensive information as a basis for providing care to newborns. A thorough understanding of normal physiology as well as the pathophysiology of disease processes is necessary for well-designed care practices. Knowledge about associated risk factors, genetics, critical periods of development, principles of nutrition and pharmacology, and current neonatal research findings are all essential in providing optimal care for neonates. A newer concept called de-implementation refers to the science of abandoning and unlearning practices built on the scaffolding of habit. Practices that are novel but yet not fully tested, unproven practices (those that lack supporting evidence), and practices of habit (practices that continue despite contradictory evidence) should go through the process of de-implementation. Care practices need to be based on best evidence-based practices available, rather than on tradition and habits.

A multidisciplinary approach has been replaced by an integrated interprofessional approach to care. All these elements form the foundation for assessment, planning, implementation, and evaluation of the effectiveness of neonatal care. The nurse plays a vital role in the provision of integrated healthcare to newborns. During the past decade, the nurse's role has included added responsibilities, which are recognized at both the staff and advanced practice levels. For the purposes of this book, we define the roles of the neonatal staff nurse, clinical nurse specialist (CNS), and neonatal nurse practitioner (NNP).

NEONATAL STAFF NURSE

The neonatal staff nurse role requires accurate and thorough assessment skills, excellent ability to communicate with other health professionals and patients' families, and a broad understanding of physiology and pathophysiology on which to base management decisions. It requires highly developed technical skills as well as critical decision-making skills. With healthcare delivery changes, the role also requires supervision of ancillary

personnel and an informed delegation of certain patient-oriented tasks. These changes require the staff nurse to possess even better assessment skills and sound knowledge of physiology and pathophysiology than in the past because some decision-making will be done in concert with other, less highly trained personnel. Additionally, the neonatal nurse is an essential contributor to the decision-making process surrounding the care of the critically ill neonate, including involvement in the ethical challenges that may occur regarding the level of care provided. In a recent position statement (#3067) by the National Association of Neonatal Nurses (NANN; Conway-Orgel, 2016), it was recommended that nursing be a part of the multidisciplinary team that facilitates decision-making affecting the health and well-being of the infant throughout the hospital stay.

In 2014, as the professional voice of neonatal nurses, NANN published a position statement (#3061) recommending that subspecialty NICUs (Level II, III, and IV NICUs) be staffed with a sufficient number and an appropriate mix of qualified registered nurses to attend to the emergent and complex care requirements of critically ill and convalescent infants (NANN, 2014c).

CLINICAL NURSE SPECIALIST

CNSs are advanced practice registered nurses (APRNs) who have graduate preparation (master's or doctorate) in nursing. Like other APRNs, they are trained in physiology, pharmacology, and physical assessment in addition to their particular areas of specialty. CNSs are expert clinicians with advanced education and training in a specialized area of nursing practice who work in a wide variety of healthcare settings. Regardless of specialty or setting, CNSs provide leadership in clinical expertise, nursing practice, and systems innovation. CNSs provide for the diagnosis, treatment, and ongoing management of patients. CNSs diagnose, develop plans of care for, treat, and provide ongoing management of complex patients. In many states, the CNSs can prescribe medications and offer durable medical equipment and therapies. They also provide expertise and support to nurses caring for patients at the bedside, help drive practice changes throughout the organization, and ensure the use of best practices and evidence-based care to achieve the best possible patient outcomes. Research and demonstration projects have shown that the CNS role is uniquely suited to lead implementation of evidence-based quality improvement actions that also reduce cost throughout the healthcare system (National Association of Clinical Nurse Specialists, 2016).

NEONATAL NURSE PRACTITIONER

The NNP is a registered nurse with clinical expertise in neonatal nursing who has received formal education at either the master's or doctoral level, with supervised clinical experience in the management of sick newborns and their families. The NNP manages a caseload of neonatal patients with consultation, collaboration, and general supervision from a physician; however, many state legislatures are following the Institute of Medicine's (IOM's) recommendation for autonomous NNP practice by repealing restrictive practice laws, thereby increasing healthcare access for millions of patients (American Association of Nurse Practitioners, 2018; Barton Associates, 2019). As a result, NNPs have increasing authority and responsibility. Using extensive knowledge of pathophysiology, pharmacology, and physiology, the NNP exercises independent or intradependent (in collaboration with other health professionals) judgment in the assessment, diagnosis, and initiation of certain delegated medical processes and procedures. As an advanced practice neonatal nurse, the NNP is additionally involved in education, consultation, and research at various levels.

NANN and the National Association of Neonatal Nurse Practitioners (NANNP), a division of NANN, published position paper #3059, a synthesis of previous efforts, which discusses the role, preparation, and scope of practice of the neonatal APRN (NANN, 2014b). NANN and NANNP define the educational and preparation standards for those pursuing the NNP role. NANN published a position statement in 1990, reaffirmed the definition of the NNP in 2000, and in 2009 issued another position statement that defined the NNP competencies (NANN, 2009). NANN (2014a) reaffirmed these core competencies for NNPs in its *Education Standards and Curriculum Guidelines for Neonatal Nurse Practitioner Programs* in 2014, which were further elaborated upon by NANNP in the development and revision of its *Competencies and Orientation Toolkit for Neonatal Nurse Practitioners* (NANNP, 2014). In 2017, NANN and NANNP published a document describing the minimum standards necessary for preparation of NNPs, titled *Education Standards and Curriculum Guidelines for Neonatal Nurse Practitioner Programs* (NANN, 2017).

In the current practice environment, outcome measures specific to the NNP must now be incorporated into professional requirements. To guide the process of continuous practice evaluation, individual practice standards have been provided by The Joint Commission in the form of ongoing professional practice evaluation or as focused professional practice evaluation (The Joint Commission, 2015). To accomplish this goal, NNPs must participate, direct, and develop performance metrics to evaluate their individual (direct) and collaborative (aggregate) contributions to improving patient and family care and outcomes while demonstrating decreased healthcare expenditures (Snapp, Wilson, Puchalski, & Wallace, 2016). Developing these outcome evaluation tools and processes will assist in the benchmarking and validation of care provided by NNPs.

The American Association of Colleges of Nurses (AACN) has proposed a change in the educational preparation for APRNs. The proposal recommends that the nurse practitioner be prepared at a "doctor of nursing practice" (DNP) level. This will likely affect the NNP role, as well as other APRNs, over the next few years.

PURPOSE AND CONTENT

The book's sixth edition provides a comprehensive assessment and examination of the care of neonates from a physiologic and pathophysiologic approach appropriate for any health professional concerned with neonatal care.

This text provides a complete physiologic and embryologic foundation for each neonatal body system. Additionally, it includes medical, surgical, and psychosocial care because the integrative management approach is absolutely imperative to the well-being of the newborn and family. Appropriate diagnostic tests and their interpretation are included in each organ-system chapter. There is extensive use of research findings in the chapters to provide evidence to support practice strategies and demonstrate the rationale for clinical decision-making. Complete references for more in-depth reading are found at the end of each chapter so that the reader may pursue more specific information on a topical area. Use of tables and illustrations further supports material that is presented in the narrative portions. New to this edition are special emergency alerts, quality and/or safety issues, and parent

voices, which are infused into applicable chapters. New chapters include Neonatal Abstinence Syndrome, The NICU—Through a Mother's Eyes (interview with a mother), and Touch a Life, Impact a Lifetime: Trauma-Informed Care in the NICU.

In the United States, the economic impact of preterm births is well over $25 billion per year (Behrman & Butler, 2007). Greater cost savings can be derived from technology that reduces labor costs, as NICU RN and respiratory therapy labor expenses account for over 60% of total neonatal care (Rhine, 2016). Now more than ever, neonatal care providers must examine patient, family, and staff outcomes to meet the demands for providing cost-effective and high-quality care. Research is critical to support both the art and science of neonatal care. Whenever possible, the contributors remind the reader of areas in need of further study. This book is not a quick reference; it provides comprehensive in-depth discussions along with detailed physiologic principles and collaborative management strategies. It provides a sound basis for safe and effective neonatal care; however, the format should make the information easier to find.

We begin the sixth edition with the impact of environmental influences and critical periods on the developing fetus. This transitions into the aspects of perinatal care, the high-risk pregnancy, the effects of labor on the fetus, and postpartal risk factors. The text then focuses on more specific neonatal topics, starting with resuscitation and stabilization of the newborn, assessment of the newborn and infant, followed by the normal term infant. Each organ system is discussed in depth, including the respiratory system, its complications and new technologies, followed by assessment of, and management strategies for, the cardiovascular, gastrointestinal, metabolic, endocrine, immunologic, integumentary, hematopoietic, musculoskeletal, neurologic, auditory, ophthalmic, and genitourinary systems. The thread of integrative management is interwoven throughout the text. Foundational topics such as fluids, electrolytes, and acid–base balance, nutrition management, pharmacology, and pain management, as well as emerging technologies and healthcare simulation are included, in addition to fetal therapy, surgical considerations, and emerging infections. Vulnerable populations cared for frequently in NICU settings are included, such as infants undergoing transplants, extremely low birth weight infants, late preterm infants, and unfortunately a growing population of infants withdrawing from opioids/neonatal abstinence syndrome. Chapters addressing environmental health and family-centered care in the NICU and beyond include neurobehavioral development, management of the NICU environment, trauma-informed care, family partnerships, palliative and end-of-life care, postdischarge care of the newborn, and, new to this section, the NICU through a mother's eyes. The final group of chapters covers neonatal care in the new millennium with topics including trends in neonatal care delivery, informatics, human genetics and genomics, trends in neonatal research and evidence-based practice, legal issues, global perspectives in neonatal care, and competency-based education and continuous competency. The sixth edition recognizes that neonatal nursing and care are global issues. The last section includes neonatal diagnostic and evidence-based care protocols pulled out separately, so they are easy to find and use. New protocols introduced in the sixth edition include neuroprotective interventions and neuroprotection of skin-to-skin contact.

To provide depth to these topical areas, physicians, nurses, infant developmental specialists, and other health professionals concerned with neonatal care from across the country and around the world have contributed in all editions. The attempt was made not only to tap the experts in the neonatal field but also to have them represent as wide a geographic area as possible. We hope that the broad geographic distribution of contributors and reviewers will help minimize the effect of regional differences in clinical practice.

We hope that you will find the text's information very useful and helpful to you in providing high-quality care to newborns and their families.

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Leslie B. Altimier
Marina V. Boykova

RECOMMENDED READINGS

American Nurses Association. (2015). *Code of ethics for nurses with interpretive statements*. Silver Spring, MD: Author.

Institute of Medicine. (2011). *The future of nursing: Leading change, advancing health* (pp. 163–220). Washington, DC: National Academies Press.

National Governors Association. (2012). *Nurse practitioners have potential to improve access to primary care*. Retrieved from https://classic.nga.org/cms/home/news-room/news-releases/page_2012/col2-content/nurse-practitioners-have-potenti.html

Prasad, V., & Ioannidis, J. P. (2014). Evidence-based de-implementation for contradicted, unproven, and aspiring healthcare practices. *Implementation Science, 9*, 1. doi:10.1186/1748-5908-9-1

REFERENCES

American Association of Nurse Practitioners. (2018). *State practice environment*. Retrieved from https://www.aanp.org/legislation-regulation/state-legislation/state-practice-environment

Barton Associates. (2019). *Nurse practitioner scope of practice laws*. Retrieved from https://www.bartonassociates.com/nurse-practitioners/nurse-practitioner-scope-of-practice-laws

Behrman, R. E., & Butler, A. S. (Eds.). (2007). *Preterm birth: Causes, consequences, and prevention*. Washington, DC: National Academies Press.

Claure, N., & Bancalari, E. (2015). Oxygen saturation targeting by automatic control of inspired oxygen in premature infants. *NeoReviews, 16*, e406–e412. doi:10.1542/neo.16-7-e406

Conway-Orgel, M. (2016). *Position statement #3067: NICU nurse involvement in ethical decisions (treatment of critically ill newborns)*. Chicago, IL: National Association of Neonatal Nurses. Retrieved from http://nann.org/uploads/3067_NICU_Nurse_Involvement_in_Ethical_Decisions.pdf

Hütten, M. C., Goos, T. G., Ophelders, D., Nikiforou, M., Kuypers, E., Willems, M., . . . Kramer, B. W. (2015). Fully automated predictive intelligent control of oxygenation (PRICO) in resuscitation and ventilation of preterm lambs. *Pediatric Research, 78*, 657–663. doi:10.1038/pr.2015.158

The Joint Commission. (2015). *Standards BoosterPak™ for focused professional practice evaluation/ongoing professional practice evaluation (FPPE/OPPE)*. Oakbrook Terrace, IL: Author.

National Association of Clinical Nurse Specialists. (2016). *Key findings from the 2016 Clinical Nurse Specialists Consensus*. Retrieved from https://nacns.org/wp-content/uploads/2016/11/2016-CNS-Census-Findings.pdf

National Association of Neonatal Nurse Practitioners. (2014). *Competencies & orientation toolkit for neonatal nurse practioners* (2nd ed.). Chicago, IL: National Association of Neonatal Nurses.

National Association of Neonatal Nurses. (2009). Position statement #3042: Requirements for advanced neonatal nursing practice in neonatal intensive care units. *Advances in Neonatal Care, 9*(4), 190–194. doi:10.1097/ANC.0b013e3181b0129a

National Association of Neonatal Nurses. (2014a). *Educaton standards and curriculum guidelines for neonatal nurse practitioner programs*.

Chicago, IL: Author. Retrieved from http://nann.org/uploads/About/PositionPDFS/1.4.8_Education%20Standards%20and%20Curriculum%20Guidelines%20for%20Neonatal%20Nurse%20Practitioner%20Programs.pdf

National Association of Neonatal Nurses. (2014b). *Position statement #3059: Advanced practice registered nurse: Role, preparation, and scope of practice*. Chicago, IL: Author. Retrieved from http://nann.org/uploads/Membership/NANNP_Pubs/APRN_Role_Preparation_position_statement_FINAL.pdf

National Association of Neonatal Nurses. (2014c). *Position statement #3061: RN staffing in the neonatal intensive care unit*. Chicago, IL: Author. Retrieved from http://nann.org/uploads/About/PositionPDFS/1.4.6_RN%20Staffing%20in%20the%20NICU.pdf

National Association of Neonatal Nurses. (2017). *Educaton standards and curriculum guidelines for neonatal nurse practitioner programs*. Chicago, IL: Author. Retrieved from http://nann.org/uploads/2017_NNP_Education_Standards_completed_FINAL.pdf

Rhine, W. D. (2016). Technology—Considerations for the NICU of the future. *Newborn and Infant Nursing Reviews, 16*(4), 208–212. doi:10.1053/j.nainr.2016.09.005

Snapp, B., Wilson, J., Puchalski, M., & Wallace, T. (2016). *Position statement #3068: Quality metrics* (Approved by the NANN Board of Directors and the NANNP Council). Chicago, IL: National Association of Neonatal Nurses. Retrieved from http://nann.org/uploads/Quality_Metrics_Position_Statement_Final.pdf

Stein, H., & Firestone, K. (2014). Application of neurally adjusted ventilatory assist in neonates. *Seminars in Fetal and Neonatal Medicine, 19*, 60–69. doi:10.1016/j.siny.2013.09.005

Acknowledgments

The idea for this book was born in the basement office of the lead editor (Dr. Carole Kenner) in Cincinnati, Ohio. In 1992, we recognized there was not a comprehensive book about nursing care for neonates. The first edition of the book was created in 1993. Over the course of the next two decades, we have refined the content to reflect new trends in neonatal care. This edition has two new editors who are committed to excellence in neonatal nursing care. I am grateful to Drs. Leslie Altimier and Marina Boykova for taking this journey with me.

Carole Kenner

Share

Comprehensive Neonatal Nursing Care

CHAPTER 1

Fetal Development: Environmental Influences and Critical Periods

Carole Kenner

INTRODUCTION

In this chapter, the major events of prenatal development are described, and critical development periods for the major organ systems are identified. A brief review of the events beginning with fertilization is included, but the reader is referred to an embryology text for a more thorough account. Human genetics is discussed in Chapter 40, Human Genetics and Genomics: Impact on Neonatal Care.

EARLY FETAL DEVELOPMENT

The process of human development begins with the fertilization of an ovum (female gamete) by a spermatocyte (male gamete). The fusion of the ovum and sperm initiates a sequence of events that causes the single-celled zygote to develop into a new human being. During the 38 to 42 weeks of gestation, dramatic growth and development occur that are unequaled during any other period of life.

Fertilization

Large numbers of spermatozoa are necessary to increase the chances for conception because the spermatozoa must traverse the cervical canal, uterus, and uterine (fallopian) tubes to reach the ovum; approximately 200 to 600 million sperm are deposited in the posterior fornix of the vagina during ejaculation. The usual site of fertilization is in the ampulla, the widest portion of the uterine tubes, located near the ovaries. Sperm are propelled by the movement of the tails, aided by muscular contractions of the uterus and fallopian tubes. The spermatozoa undergo two physiologic changes to penetrate the corona radiata and zona pellucida, the barriers around the secondary oocyte. The first change is capacitation, an enzymatic reaction that removes the glycoprotein coating from the spermatozoa and plasma proteins from the seminal fluid. Capacitation generally occurs in the uterus or uterine tubes and takes about 7 hours. The second change, the acrosome reaction, occurs when a capacitated sperm passes through the corona radiata, causing structural changes that result in the fusion of the plasma membranes of the sperm and the oocyte. Progesterone released from the follicle at ovulation stimulates the acrosome reaction. Three enzymes are released from the acrosome to facilitate entry of the sperm into the ovum. Hyaluronidase allows the sperm to penetrate the corona radiata, whereas trypsin-like enzymes and zona lysin digest a pathway across the zona pellucida (Moore, Persaud, & Torchia, 2015; Sadler, 2015).

Only about 300 to 500 spermatozoa actually reach the ovum. When a spermatozoon comes into contact with the ovum, the zona pellucida and the plasma membrane fuse, preventing entry by other sperm. After penetration by a single sperm, the oocyte completes the second meiotic cell division, resulting in the haploid number of chromosomes (22,X) and the second polar body. The chromosomes are arranged to form the female pronucleus (Moore et al., 2015; Sadler, 2015).

As the spermatozoon moves close to the female pronucleus, the tail detaches, and the nucleus enlarges to form the male pronucleus. The male and female pronuclei fuse forming a diploid cell called the zygote. The zygote contains 23 autosomes and 1 sex chromosome from each parent (46,XX or 46,XY). The genetic sex of the new individual is determined at fertilization by the contribution of the father. The male parent (XY) may contribute either an X or a Y chromosome. If the spermatozoon contains an X chromosome, the offspring is female (46,XX). If the spermatozoon receives one Y chromosome, the offspring is male (46,XY). Individual variation is the result of random or independent assortment of the autosomal chromosomes (Moore et al., 2015; Sadler, 2015).

Cleavage

Mitotic cell division occurs after fertilization as the zygote passes down the uterine tube, resulting in the formation of two blastomeres (Figure 1.1). The cells continue to divide, increasing in number, although decreasing in size. The term *cleavage* is used to describe the mitotic cell division of the zygote (Figure 1.2). When the number of cells reaches approximately 16 (usually on the third day), the zygote is called a morula, because of its resemblance to a mulberry. The zygote reaches the morula stage about the time it enters the uterus. The morula consists of groups of centrally located cells called the inner cell mass and an outer cell layer. At this stage, the individual cells are called blastomeres. The outer cell layer forms the trophoblast, from which the placenta develops. The inner cell mass, called the embryoblast, gives rise to the embryo (Moore et al., 2015; Sadler, 2015).

After the morula penetrates the uterine cavity, fluid enters through the zona pellucida into the intercellular spaces of the inner cell mass. The fluid-filled spaces fuse, forming a large cavity known as the blastocyst cavity about the fourth day after fertilization. The morula is now called the blastocyst. This outer cell layer, known

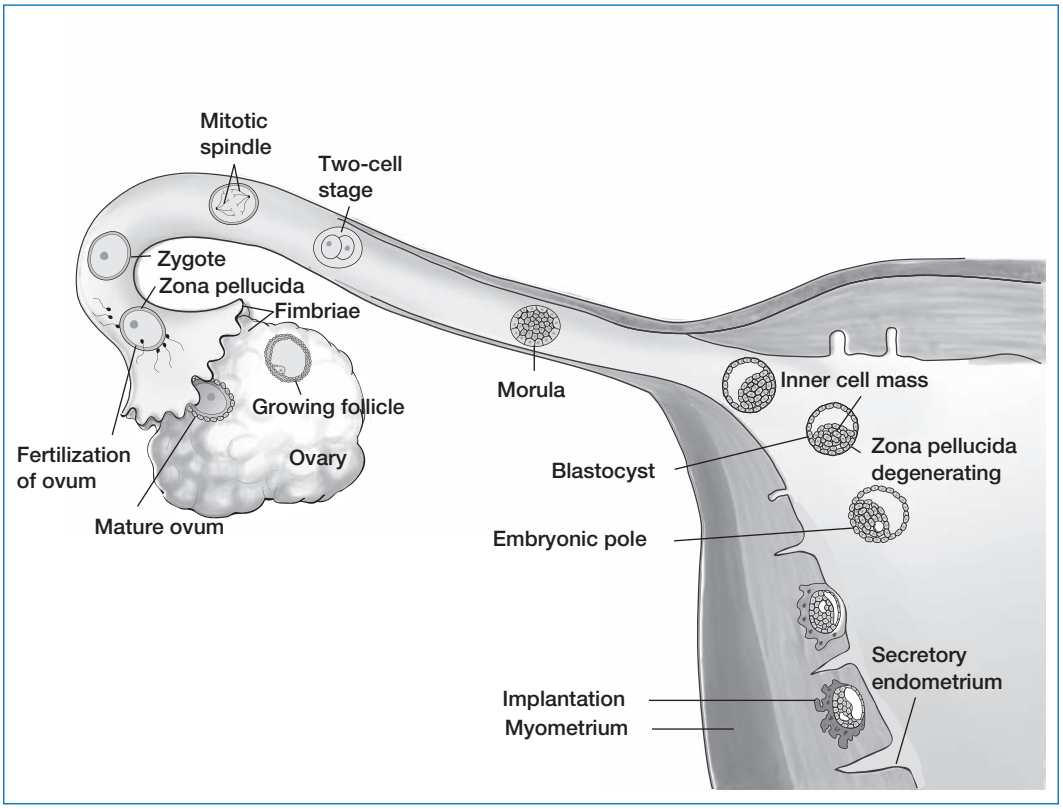


FIGURE 1.1 Fantastic voyage. From fertilization to implantation. The journey through the fallopian tubes takes approximately 4 days. During this time, mitotic cell division occurs. Implantation occurs on about day 9 through 12.

as the trophoblast, forms the wall of the blastocyst, which later becomes the placenta, and the embryoblast projects from the wall of the blastocyst into the blastocyst cavity. The uterine secretions nourish the blastocyst until implantation occurs (Moore et al., 2015; Sadler, 2015).

Implantation

Degeneration of the zona pellucida occurs on about the fifth day after fertilization, allowing the blastocyst to attach to the endothelium of the endometrium on about the sixth day. The trophoblasts then secrete proteolytic enzymes that destroy the endometrial endothelium and invade the endometrium. Two layers of trophoblasts develop; the inner layer is made up of cytotrophoblasts, and the outer layer is composed of syncytiotrophoblasts. The syncytiotrophoblast has finger-like projections that produce enzymes capable of further eroding the endometrial tissues. By the end of the seventh day, the blastocyst is superficially implanted (Figure 1.3).

Formation of the Bilaminar Disk

Implantation is completed during the second week. The syncytiotrophoblast continues to invade the endometrium and becomes embedded. Spaces in the syncytiotrophoblast, called lacunae, fill with blood from ruptured maternal capillaries and secretions from eroded endometrial glands. This fluid nourishes the embryoblast by diffusion. The lacunae give rise to the uteroplacental circulation. The lacunae fuse to form a network that then becomes the intervillous spaces of the placenta. The endometrial capillaries near the implanted embryoblast become dilated and eroded by the syncytiotrophoblast. Maternal blood enters the lacunar network and provides circulation and nutrients to the embryo. Maternal embryonic blood circulation provides the developing embryo with nutrition and oxygenation and removes waste products before the development of the placenta. Finger-like projections, primary chorionic villi, of the chorion develop into the chorionic villi of the placenta at about the same time (Moore et al., 2015; Sadler, 2015).

The inner cell mass differentiates into two layers: the hypoblast (endoderm), a layer of small cuboidal cells, and the epiblast (ectoderm), a layer of high columnar cells. The two layers form a flattened, circular bilaminar embryonic disk. The amniotic cavity is derived from spaces within the epiblast. As the amniotic cavity enlarges, a thin layer of epithelial cells covers the amniotic cavity. During the development of the amniotic cavity, other trophoblastic cells form a thin extracoelomic membrane, which encloses the primitive yolk sac. The yolk sac produces fetal red blood cells. Other trophoblastic cells form a layer of mesenchymal tissue, called the extraembryonic mesoderm, around the amnion and primitive yolk sac. Isolated coelomic spaces in the extraembryonic mesoderm fuse to form a single, large, fluid-filled cavity surrounding the amnion and yolk sac, with the exception of the area where the amnion is attached to the chorion by the connecting stalk. The primitive yolk sac decreases in size, creating a smaller secondary yolk sac (Moore et al., 2015; Sadler, 2015).

Two layers of extraembryonic mesoderm result from the formation of the extraembryonic cavity. The extraembryonic somatic mesoderm lines the trophoblast and covers the amnion, and the extraembryonic splanchnic mesoderm covers the yolk sac. The chorion is made up of the extraembryonic somatic mesoderm, the cytotrophoblast, and the syncytiotrophoblast. The chorion forms the chorionic sac, in which the embryo, the amniotic sac, and the yolk sac are located. By the end of the second week, there is a slightly thickened area near the cephalic region of the hypoblastic disk, known as the prochordal plate, which marks the location of the mouth (Moore et al., 2015; Sadler, 2015).

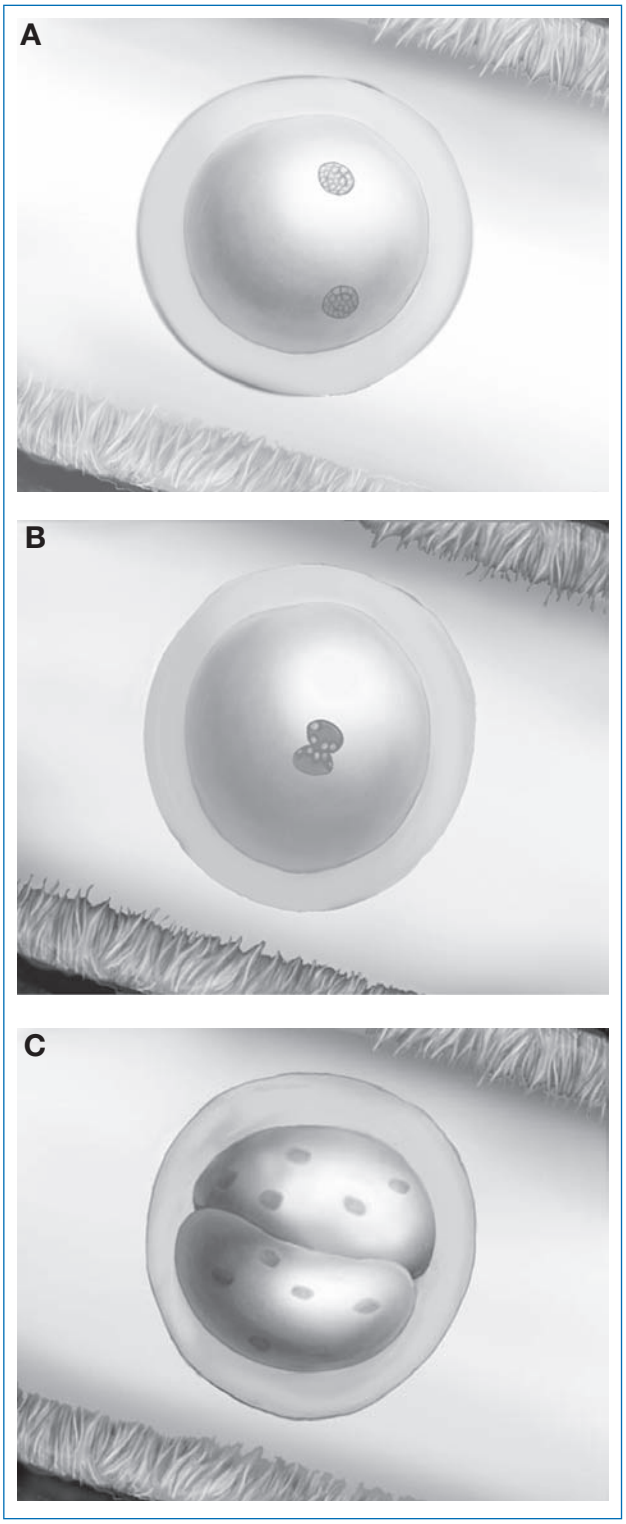


FIGURE 1.2 Stages of cell division: cleavage. (A) Zygote. (B) Zygote undergoing first cleavage. (C) Two-cell blastomere state.

Formation of the Trilaminar Embryonic Disk: The Third Week of Development

The third week of development is marked by rapid growth, the formation of the primitive streak, and the differentiation of the three germ layers, from which all fetal tissue and organs are derived (Moore et al., 2015; Sadler, 2015; Figure 1.4).

Gastrulation. Gastrulation is the process through which the bilaminar disk develops into a trilaminar embryonic disk.

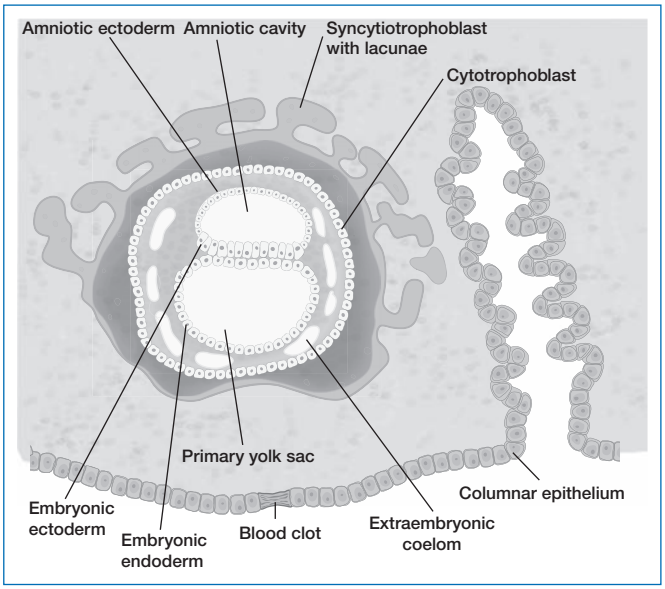


FIGURE 1.3 Cross section of a blastocyst at 11 days. Two germ layers are present. The trophoblast has differentiated into the syncytiotrophoblast and the cytotrophoblast.

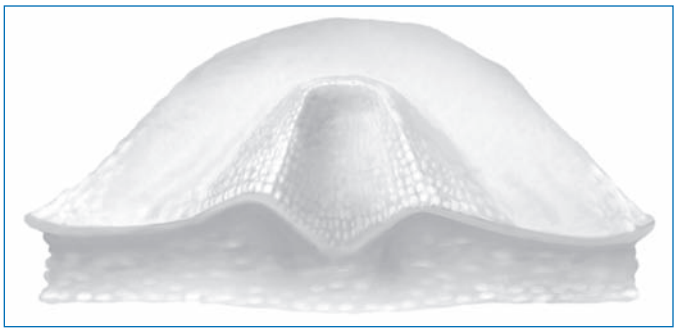


FIGURE 1.4 Formation of the trilaminar embryonic disk: gastrulation. During gastrulation, the bilaminar embryonic disk changes to a trilaminar embryonic disk, consisting of the epiblast (ectoderm), hypoblast (endoderm), and mesoblast (mesoderm).

Gastrulation is the most important event of early fetal formation; it affects all of the rest of embryologic development. During the third week, epiblast cells separate from their original location and migrate inward, forming the mesoblast, which spreads cranially and laterally to form a layer between the ectoderm and the endoderm called the intraembryonic mesoderm. Other mesoblastic cells invade the endoderm, displacing the endodermal cells laterally, forming a new layer, the embryonic ectoderm. Thus, the hypoblastic ectoderm produces the embryonic ectoderm, embryonic mesoderm, and the majority of the embryonic endoderm. These three germ layers are the source of the tissue and organs of the embryo (Moore et al., 2015; Sadler, 2015).

Primitive Streak. Over days 14 and 15, a groove and thickening of the ectoderm (epiblast), called the primitive streak, appears caudally in the center of the dorsum of the embryonic disk. The primitive streak results from the migration of ectodermal cells toward the midline in the posterior portion of the embryonic disk. The primitive groove develops in the primitive streak. When the primitive streak begins to produce mesoblastic cells that become intraembryonic mesoderm, the epiblast is referred to as the embryonic ectoderm and the hypoblast is referred to as the embryonic mesoderm (Moore et al., 2015; Sadler, 2015).

Notochordal Process. Cells from the primitive knot migrate cranially and form the midline cellular notochordal process. This process grows cranially between the ectoderm and the endoderm until it reaches the prochordal plate, which is attached to the overlying ectoderm, thus forming the oropharyngeal membrane. The cloacal membrane, caudal to the primitive streak, develops into the anus (Moore et al., 2015; Sadler, 2015).

The primitive streak produces mesenchyme (mesoblasts) until the end of the fourth week. The primitive streak does not grow as rapidly as the other cells, making it relatively insignificant in size when compared with the other structures that continue to grow. Persistence of the primitive streak or remnants is the cause of sacrococcygeal teratomas (Moore et al., 2015; Sadler, 2015).

The notochord, a cellular rod that develops from the notochordal process, is the structure around which the vertebral column is formed. It forms the nucleus pulposus of the intervertebral bodies of the spinal column (Figure 1.5; Moore et al., 2015; Sadler, 2015).

Neurulation. Neurulation is the process through which the neural plate, neural folds, and neural tube are formed. The developing notochord stimulates the embryonic ectoderm to thicken, forming the neural plate. The neuroectoderm of the neural plate gives rise to the central nervous system (CNS). The neural plate develops cranial to the primitive knot. As the neural plate elongates, it gets wider and extends cranially to the oropharyngeal membrane. The neural plate invaginates along the central axis to form a neural groove with neural folds on each side. The neural folds move together and fuse, forming the neural tube showing the first indication of brain development (Figure 1.6). The neural tube detaches from the surface ectoderm, and the free edges of the ectoderm fuse, covering the posterior portion of the embryo. With formation of the neural tube, nearby ectodermal cells lying along the crest of each neural fold migrate inward, invading the mesoblast on each side of the neural tube. These irregular, flattened masses are called the neural crest. This structure's cells give rise to the spinal ganglia, the ganglia of the autonomic nervous system, and cranial nerves V, VII, IX, and X. Neural crest cells also form the meningeal covering of the brain and spinal cord and the sheaves that protect nerves. The neural crest cells contribute to the formation of pigment-producing cells, the adrenal medulla, and skeletal and muscular development in the head (Moore et al., 2015; Sadler, 2015).

Development of Somites. Another important event of the third week is the development of somites, which give rise to most of the skeleton and associated musculature and much of the dermis of the skin. During formation of the neural tube, the intraembryonic mesoderm on each side thickens, forming longitudinal columns of paraxial mesoderm. At about 20 days, the paraxial mesoderm begins to divide into paired cuboidal bodies known as somites. In all, 42 to 44 somites develop, in a craniocaudal sequence, although only 38 develop during the "somite" period. These somite pairs can be counted and give an estimate of fetal age before a crown-rump (C-R) measurement is possible (Moore et al., 2015; Sadler, 2015).

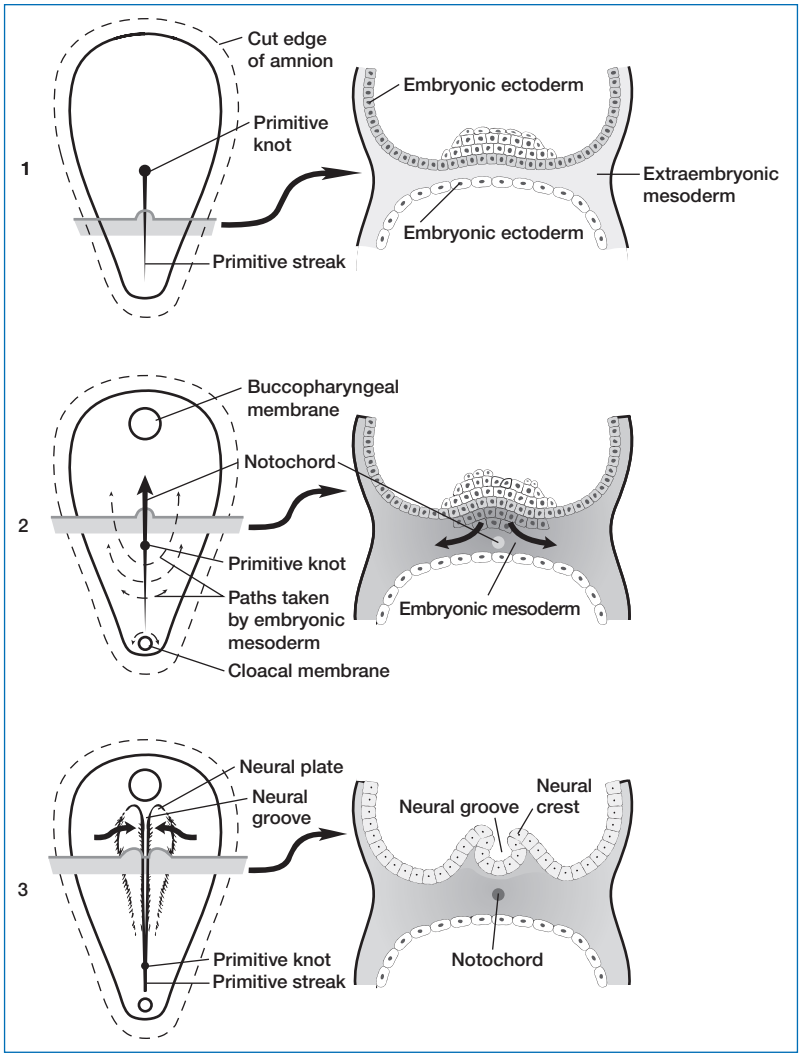


FIGURE 1.5 Formation of primitive streak, primitive knot, notochord, and neural groove.

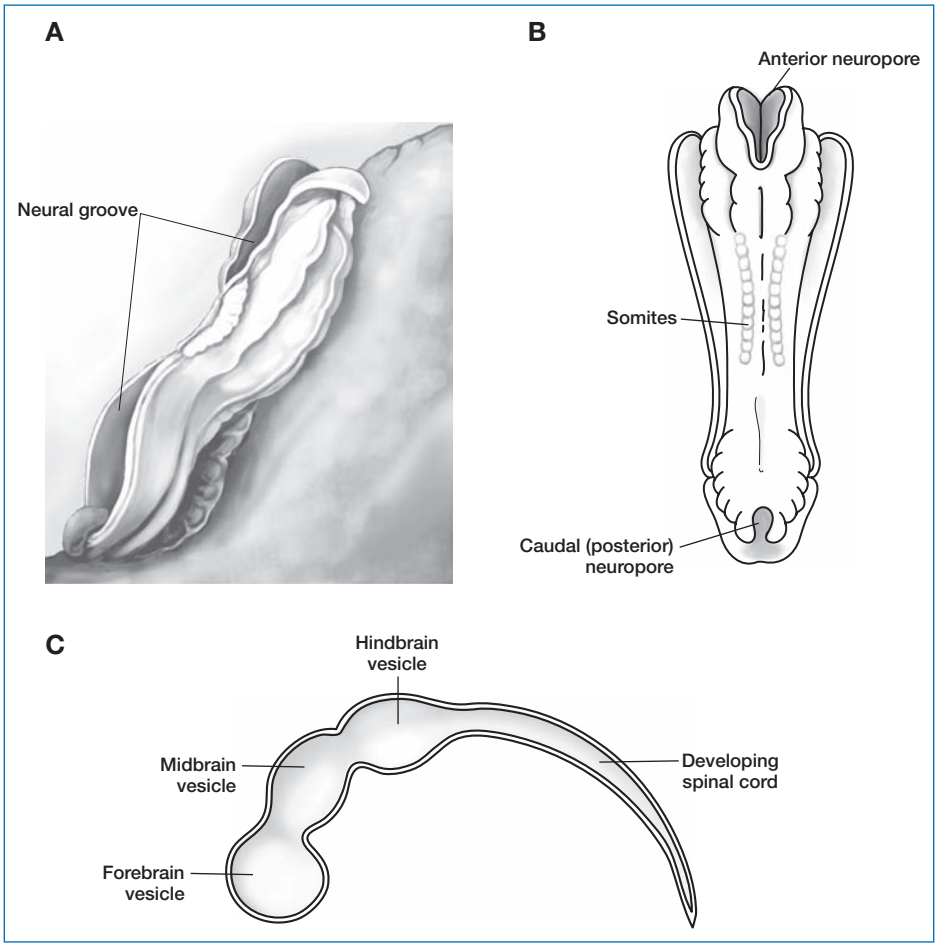


FIGURE 1.6 Formation of the neural tube. (A) Neural groove. (B) Closure of the neural tube almost completed. (C) Dilation of the neural tube forms the forebrain, midbrain, and hindbrain.

Intraembryonic Cavity. Another significant process is the formation of the intraembryonic cavity. This structure first appears as a number of small spaces within the lateral mesoderm and the cardiogenic mesoderm. These spaces combine to form the intraembryonic cavity; it is horseshoe-shaped and lined with flattened epithelial cells that eventually line the peritoneal cavity. The intraembryonic cavity divides the lateral mesoderm into the parietal (somatic) and visceral (splanchnic) layers. It gives rise to the pericardial cavity, the pleural cavity, and the peritoneal cavity (Moore et al., 2015; Sadler, 2015).

PLACENTAL DEVELOPMENT AND FUNCTION

The rudimentary maternal fetal circulation is intact by the fourth week of gestation. Growth of the trophoblast results in numerous primary and secondary chorionic villi, covering the surface of the chorionic sac until about the eighth week of gestation. At about the eighth week, the villi overlying the conceptus (decidua capsularis) degenerate, leaving a smooth area (smooth chorion). The villi underlying the conceptus (decidua basalis) remain and increase in size, producing the chorion frondosum, or fetal side of the placenta. The maternal side of the placenta is made up of the chorion and the chorionic villi. On implantation of the conceptus, maternal capillaries of the decidua basalis rupture, causing maternal blood to circulate through the developing fetal placenta (chorion frondosum). As growth and differentiation progress, extensions from the cytotrophoblast invade the syncytial layer and form a cytotrophoblastic shell, surrounding the conceptus and chorionic villi. This shell is continuous, but has communications between maternal blood vessels in the decidua basalis and the intervillous spaces of the chorion frondosum. The latter is attached to the maternal side of the placenta (decidua basalis) by the cytotrophoblastic shell and anchoring villi. The placenta is mature and completely functional by 16 weeks of development (Figure 1.7). If the corpus luteum begins to regress prior to the 16th week and fails to produce enough progesterone (the hormone responsible for readying the uterine cavity for the pregnancy), the pregnancy is aborted because the placenta is not capable of supporting the pregnancy on its own until about this time (Moore et al., 2015; Sadler, 2015).

Placental Fetal Circulation

A simple ebb-and-flow circulation is present in the embryo, yolk sac, connecting stalk, and chorion by 21 days of gestation. By 28 days, unidirectional circulation is established. Deoxygenated fetal blood leaves the fetus via the umbilical arteries and enters the capillaries in the chorionic villi, where gaseous and nutrient exchanges take place. Oxygenated blood returns to the fetus through the umbilical veins. At first, there are two arteries and two veins, but one vein gradually degenerates, leaving two arteries and one vein. If only one artery is present, a congenital anomaly, especially a renal one, should be suspected (Moore et al., 2015; Sadler, 2015).

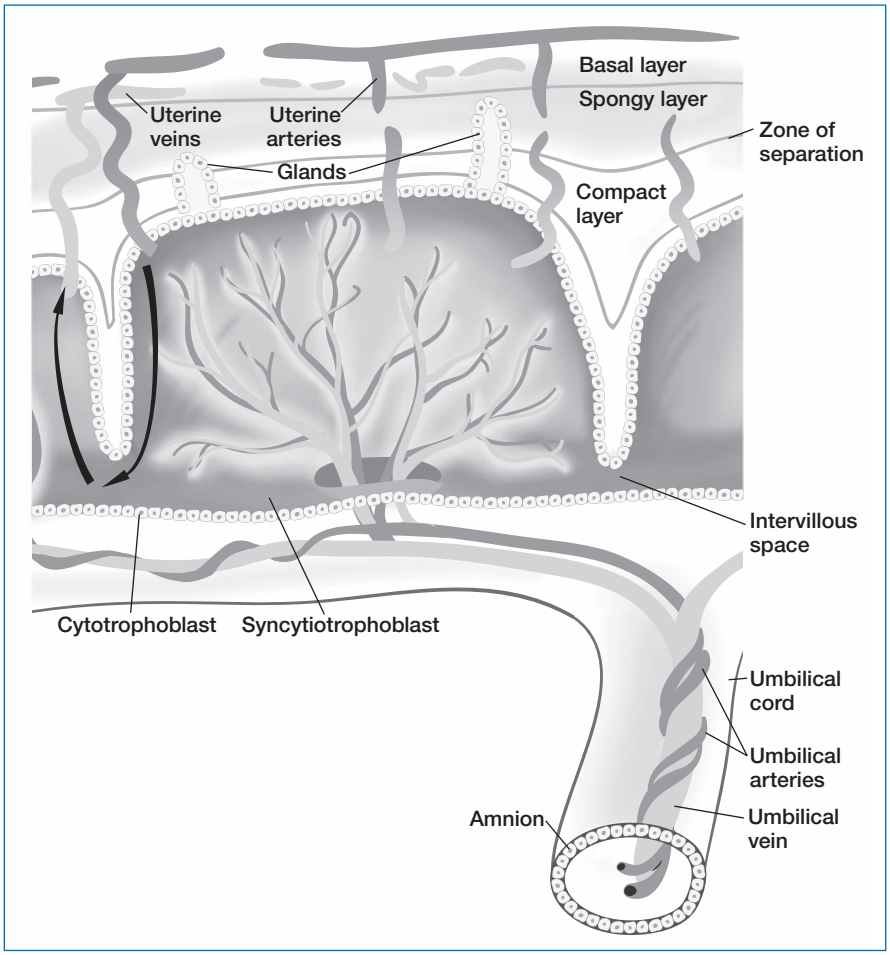


FIGURE 1.7 Formation of the placenta. The fetal and maternal sides of the placenta. Separation of the placenta from the uterus occurs at the site indicated by the gray line labeled zone of separation.

Placental Function

Normal growth and development of the embryo depend on adequate placental function. The placenta is responsible for oxygenation, nutrition, elimination of wastes, production of hormones essential for maintenance of the pregnancy, and transport of substances. In addition, the placenta synthesizes glycogen, cholesterol, and fatty acids, which provide nutrients and energy for early fetal development. Transport across the placental membrane occurs primarily through simple and facilitated diffusion, active transport, and pinocytosis. Oxygen, carbon dioxide, and carbon monoxide cross the placenta through simple diffusion. The fetus depends on a continuous supply of oxygenated blood flowing from the placenta (Moore et al., 2015; Sadler, 2015).

Water and electrolytes cross the placenta freely in both directions. Glucose is converted to glycogen in the placenta as a carbohydrate source for the fetus. Amino acids move readily across the placental membranes for protein synthesis in the fetus. Free fatty acids are transferred across the placenta by pinocytosis. There is limited or no transfer of maternal cholesterol, triglycerides, and phospholipids. Water- and fat-soluble vitamins cross the placenta and are essential for normal development (Moore et al., 2015; Sadler, 2015).

The placenta produces and transports hormones that maintain the pregnancy and promote growth and development of the fetus. Chorionic gonadotropin, a protein hormone produced by the syncytiotrophoblast, is excreted in maternal serum and urine. The presence of human chorionic gonadotropin is used as a test for pregnancy. Human placental lactogen, also a protein hormone produced by the placenta, acts as a fetal growth–promoting hormone by giving the fetus priority for receiving maternal glucose (Moore et al., 2015; Sadler, 2015).

The placenta also produces steroid hormones. Progesterone, produced by the placenta throughout gestation, is responsible for maintaining the pregnancy. Estrogen production by the placenta depends on stimulation by the fetal adrenal cortex and liver. Placental transport of maternal antibodies provides the fetus with passive immunity to certain viruses. IgG antibodies are actively transported across the placental barrier, providing humoral immunity for the fetus. IgA and IgM antibodies do not cross the placental barrier, placing the neonate at risk for neonatal sepsis. However, failure of IgM antibodies to cross the placental membrane explains the lower incidence of a severe hemolytic process in ABO blood type incompatibilities when compared with Rh incompatibilities. The latter result when an Rh-negative mother has an Rh-positive fetus. If the mother is sensitized to the Rh-positive fetal blood cells, the mother produces IgG antibodies. IgG is transferred from the maternal to fetal circulation, and hemolysis of fetal red blood cells occurs (Moore et al., 2015; Sadler, 2015).

The placenta is selective in the transfer of substances across the placenta; however, this selectivity does not screen out all potentially harmful substances. Viral, bacterial, and protozoal organisms can be transferred to the fetus through the placenta. Toxic substances such as drugs and alcohol can also be transferred to the fetus. The effects of these substances depend on the stage of gestation and type and duration of exposure, as well as the interaction of these and other factors, such as nutrition.

EMBRYONIC PERIOD: WEEKS 4 THROUGH 8

The embryonic period lasts from the beginning of gestational week 4 through the end of week 8. Organogenesis, which is the formation of all major organs, occurs during this period. The shape of the embryo changes as the organs develop, taking a more human shape by the end of the eighth week. The major events of the embryonic period are the folding of the embryo and organogenesis.

Folding of the Embryo

In the trilaminar embryonic disk, the growth rate of the central region exceeds that of the periphery so that the slower growing areas fold under the faster growing areas, forming body folds. The head fold appears first as a result of craniocaudal elongation of the notochord and growth of the brain, which projects into the amniotic cavity. The folding downward of the cranial end of the embryo forces the septum transversum (primitive heart), the pericardial cavity, and the oropharyngeal membrane to turn under onto the ventral surface. After the embryo has folded, the mass of mesoderm cranial to the pericardial cavity, the septum transversum, lies caudal to the heart. The septum transversum later develops into a portion of the diaphragm. Part of the yolk sac is incorporated as the foregut, lying between the heart and the brain. The foregut ends blindly at the oropharyngeal membrane, which separates the foregut from the primitive mouth cavity (stomodeum; Moore et al., 2015; Sadler, 2015).

The tail fold occurs after the head fold as a result of craniocaudal growth progression. Growth of the embryo causes the caudal area to project over the cloacal membrane. During the tail folding, part of the yolk sac is incorporated into the embryo as the hindgut. After completion of the head and tail folding, the connecting stalk is attached to the ventral surface of the embryo, forming the umbilical cord. Folding also occurs laterally, producing right and left lateral folds. The lateral body wall on each side folds toward the median plane, causing the embryo to assume a cylindrical shape. During the lateral body folding, a portion of the yolk sac is incorporated as the midgut. The attachment of the midgut to the yolk sac is minimal after this fold develops. After folding, the amnion is attached to the embryo in a narrow area in which the umbilical cord attaches to the ventral surface (Moore et al., 2015; Sadler, 2015).

Organogenesis: Germ Cell Derivatives

The three germ cell layers (ectoderm, mesoderm, and endoderm) give rise to all tissues and organs of the embryo. The germ cells follow specific patterns during the process of organogenesis. The main germ cell derivatives are listed in Box 1.1. The development of each major organ system is discussed separately. The embryonic period is the most critical period of development because of the formation of internal and external structures. The critical periods of development for the organs are also discussed in the section on specific organ development.

Box 1.1

GERM CELL DERIVATIVES

Ectoderm

- CNS (brain, spinal cord)
- Peripheral nervous system
- Sensory epithelia of eye, ear, and nose
- Epidermis and its appendages (hair and nails)
- Mammary glands
- Subcutaneous glands
- Teeth enamel
- Neural crest cells
- Spinal, cranial, and autonomic ganglia cells
- Nerve sheaths of peripheral nervous system
- Pigment cells
- Muscle, connective tissue, and bone of branchial arch origin
- Adrenal medulla
- Meninges

Mesoderm

- Cartilage
- Bone
- Connective tissue
- Striated and smooth muscle
- Heart, blood, and lymph vessels and cells
- Gonads
- Genital ducts
- Pericardial, pleural, and peritoneal lining
- Spleen
- Cortex of adrenal gland

Endoderm

- Epithelial lining of respiratory and gastrointestinal tracts
- Parenchyma of tonsils, thyroid, parathyroid, liver, thymus, and pancreas
- Epithelial lining of bladder and urethra
- Epithelial lining of tympanic cavity, tympanic antrum, and auditory tube

CNS, central nervous system

DEVELOPMENT OF SPECIFIC ORGANS AND STRUCTURES

Nervous System

The origin of the nervous system is the neural plate, which arises as a thickening of the ectodermal tissue about the middle of the third week of gestation. The neural plate further differentiates into the neural tube and the neural crest. The neural tube gives rise to the CNS. The neural crest cells give rise to the peripheral nervous system (Figure 1.8; Moore et al., 2015; Sadler, 2015).

The cranial end of the neural tube forms the three divisions of the brain: the forebrain, the midbrain, and the hindbrain. The

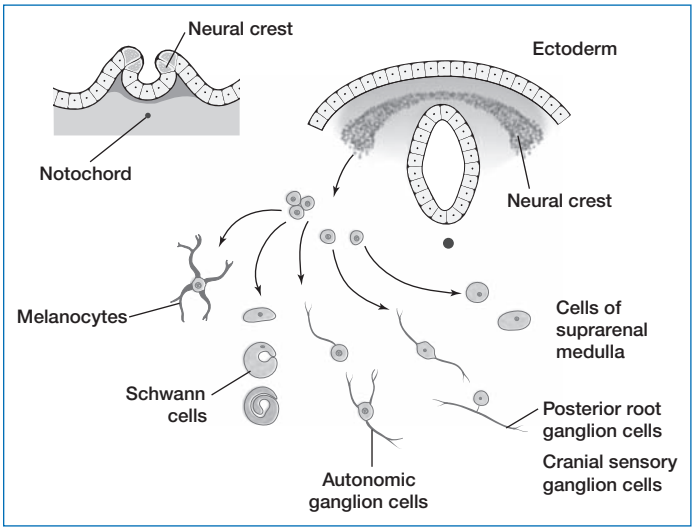


FIGURE 1.8 Differentiation of the nervous system. The cells of the neural crest differentiate into the cells of the ganglia, Schwann cells, and the cells of the suprarenal medulla and melanocytes.

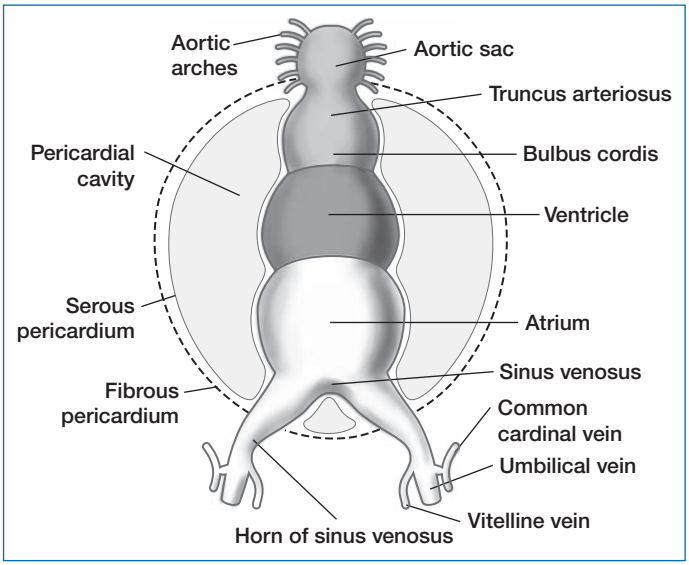


FIGURE 1.9 Formation of the single heart tube. The appearance of the single heart tube inside the pericardial cavity. Note that the atrium and sinus venosus are outside the pericardial cavity.

cerebral hemispheres and diencephalon arise from the forebrain; the pons, cerebellum, and medulla oblongata arise from the hindbrain. The midbrain makes up the adult midbrain (Moore et al., 2015; Sadler, 2015).

The cavity of the neural tube develops into the ventricles of the brain and the central canal of the spinal column. The neuroepithelial cells lining the neural tube give rise to nerves and glial cells of the CNS. The peripheral nervous system consists of the cranial, spinal, and visceral nerves and the ganglia. The somatic and visceral sensory cells of the peripheral nervous system arise from neural crest cells. Cells that form the myelin sheaths of the axons, called Schwann cells, also arise from the neural crest cells (Moore et al., 2015; Sadler, 2015).

Cardiovascular System

The fetal cardiac system appears at about 18 to 19 days of gestation, and circulation is present by about 21 days. The cardiovascular system is the first organ system to function in utero. The heart starts to beat at the beginning of the fourth week. The heart and blood develop from the middle layer (mesoderm) of the trilaminar embryonic disk. Tissue from the lateral mesoderm migrates up the sides of the embryonic disk, forming a horseshoe-shaped structure that arches and meets above the oropharyngeal membrane. With further development, paired heart tubes form, which then fuse into a single heart tube (Figure 1.9). The vessels that make up the vascular system throughout the body develop from mesodermal cells that connect to each other, with the developing heart tube and the placenta. Thus, by the end of the third week of gestation, there is a functional cardiovascular system (Moore et al., 2015; Sadler, 2015).

As the heart tube grows, the folding of the embryonic disk results in the movement of the heart tube into the chest cavity. The heart tube differentiates into three layers: the endocardial layer, which becomes the endothelium; the cardiac jelly, which is a loose tissue layer; and the myoepicardial mantle, which becomes the myocardium and pericardium. The single heart tube is attached at its cephalic end by the aortic arches and at the caudal end by the septum transversum. The attachments limit the length of the heart tube. Continued growth results in dilated areas and bulges, which become specific components of the heart. The atrium, ventricle, and bulbus cordis can be identified first, followed by the sinus venosus and truncus arteriosus. To accommodate continued growth, two separate bends in the heart occur. It first bends to the right to form a U shape, and the next bend results in an S-shaped heart. The bending of the heart is responsible for the typical location of cardiac structures (Figure 1.10; Moore et al., 2015; Sadler, 2015).

Initially, the heart is a single chamber; partitioning of the heart into four chambers occurs from the fourth to sixth weeks of gestation. The changes that cause the partitioning of the heart occur simultaneously. The atrium is separated from the ventricle by endocardial cushions, which are thickened areas of endothelium that develop on the dorsal and ventral walls of the open area between the atrium and ventricle. The endocardial cushions fuse with each other to divide the atrioventricular canals into right and left atrioventricular canals. Partitioning of the atrium occurs through invagination of tissue toward the endocardial cushions, forming the septum primum. As the septum primum grows toward the endocardial cushions, it becomes very thin and perforates, becoming the foramen ovale. The septum primum does not fuse completely with the endocardial cushions; it has a lower portion that lies beside the endocardial cushions. Overlapping of the septum primum and the septum secundum forms a wall if the pressure in both atria is equal. In utero, the pressure on the right side is increased, allowing blood to flow across the foramen ovale from the right side of the heart to the left side (Figure 1.11; Moore et al., 2015; Sadler, 2015).

The ventricle is also partitioned by a membranous and muscular septum. The muscular portion of the septum develops from the fold of the floor of the ventricle. With blood flowing through the atrioventricular canal, ventricular dilation occurs on either side of the fold or ridge, causing it to become a septum. The membranous septum arises from ridges inside the bulbus cordis. These ridges, continuous into the bulbus cordis, form the wall that divides the bulbus cordis into the pulmonary artery and the aorta. The bulbar ridges fuse with the endocardial cushions to form the membranous septum. The membranous and muscular septa fuse to close the intraventricular foramen, resulting in two parallel circuits of blood flow. The pulmonary artery is continuous with the right ventricle, and the aorta is continuous with the left ventricle (Figure 1.12; Moore et al., 2015; Sadler, 2015).

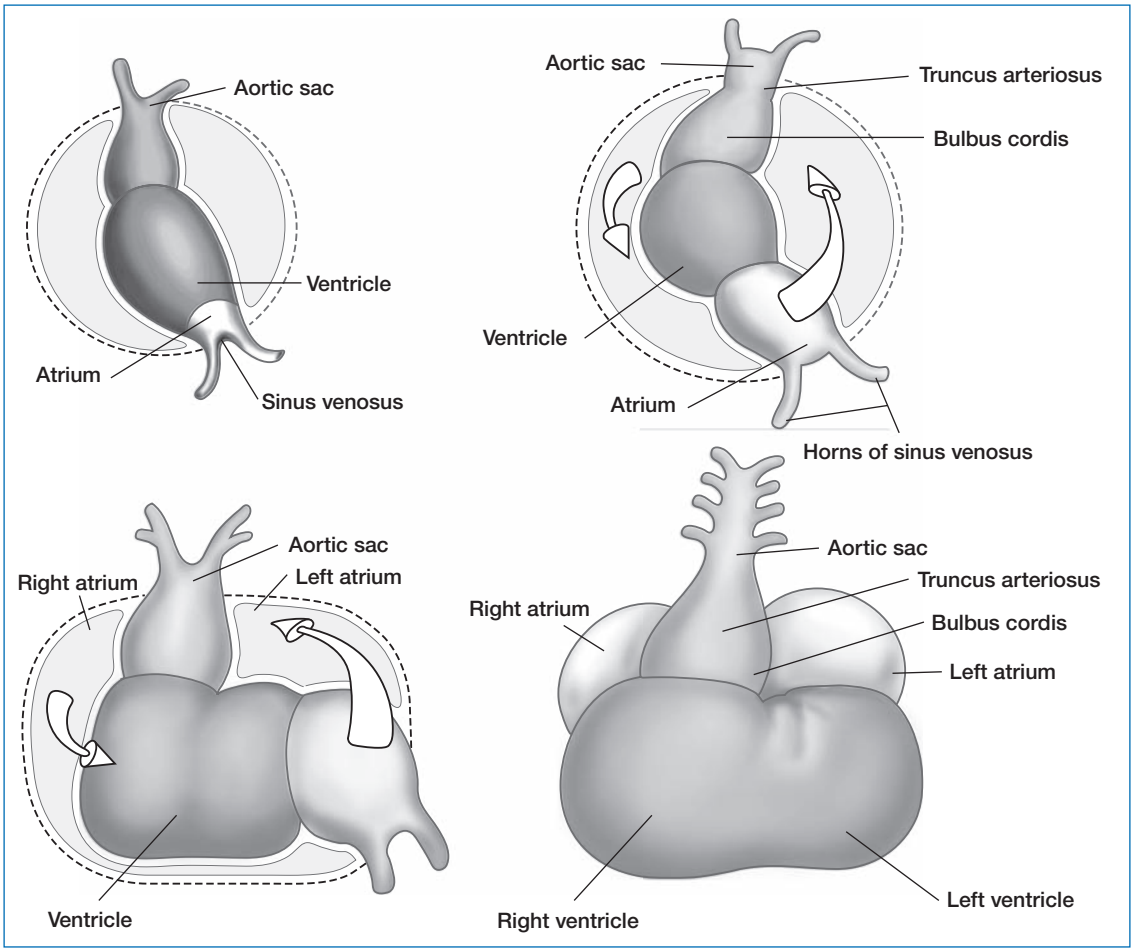


FIGURE 1.10 Bending of the heart tube inside the pericardial cavity. The bending of the heart tube brings the atrium into the pericardial cavity. The sinus venosus is taken into the right atrium and the coronary sinus.

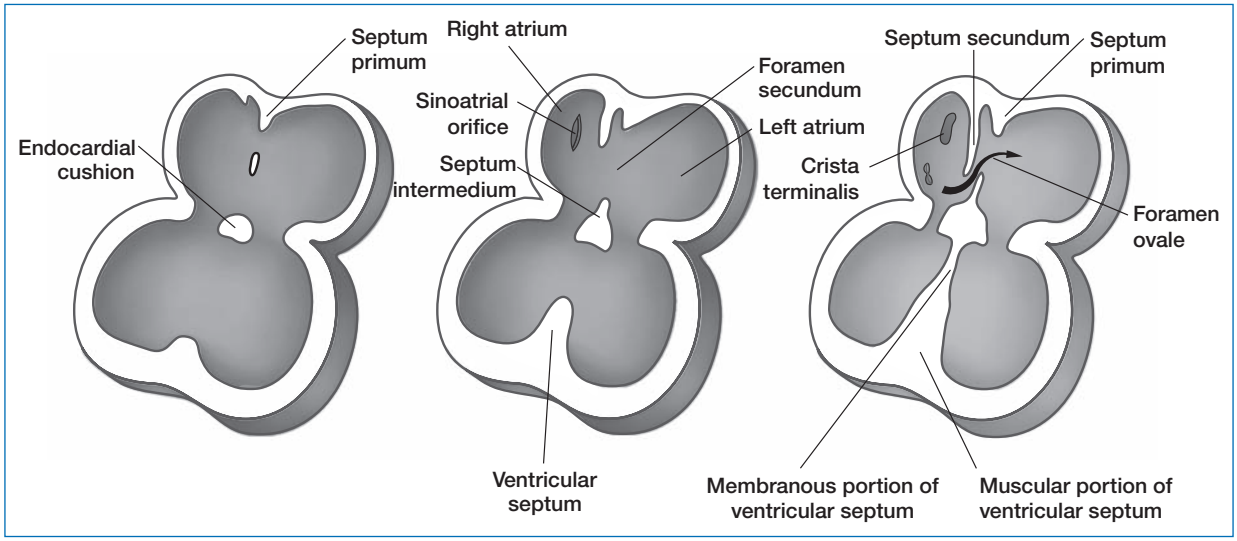


FIGURE 1.11 Partitioning of the atrium. The partitioning of the atrium into the right and left atria through septation.

The blood flowing through the bulbus cordis and truncus arteriosus in a spiral causes the formation of ridges. The ridges fuse to form two separate vessels that twist around each other once. Thus, the pulmonary artery exits the right side of the heart and is in the left upper chest; the aorta exits the left side of the heart and is located close to the sternum (Moore et al., 2015; Sadler, 2015).

The pulmonary veins grow from the lungs to a cardinal vein plexus. Concurrently, a vessel develops from the smooth wall of the left atrium. As the atrium grows, the pulmonary vein is incorporated into the atrial wall. The atrium and its branches give rise to four pulmonary veins that enter the left atrium. These pulmonary vessels, connected to the plexus of the cardinal vein, provide

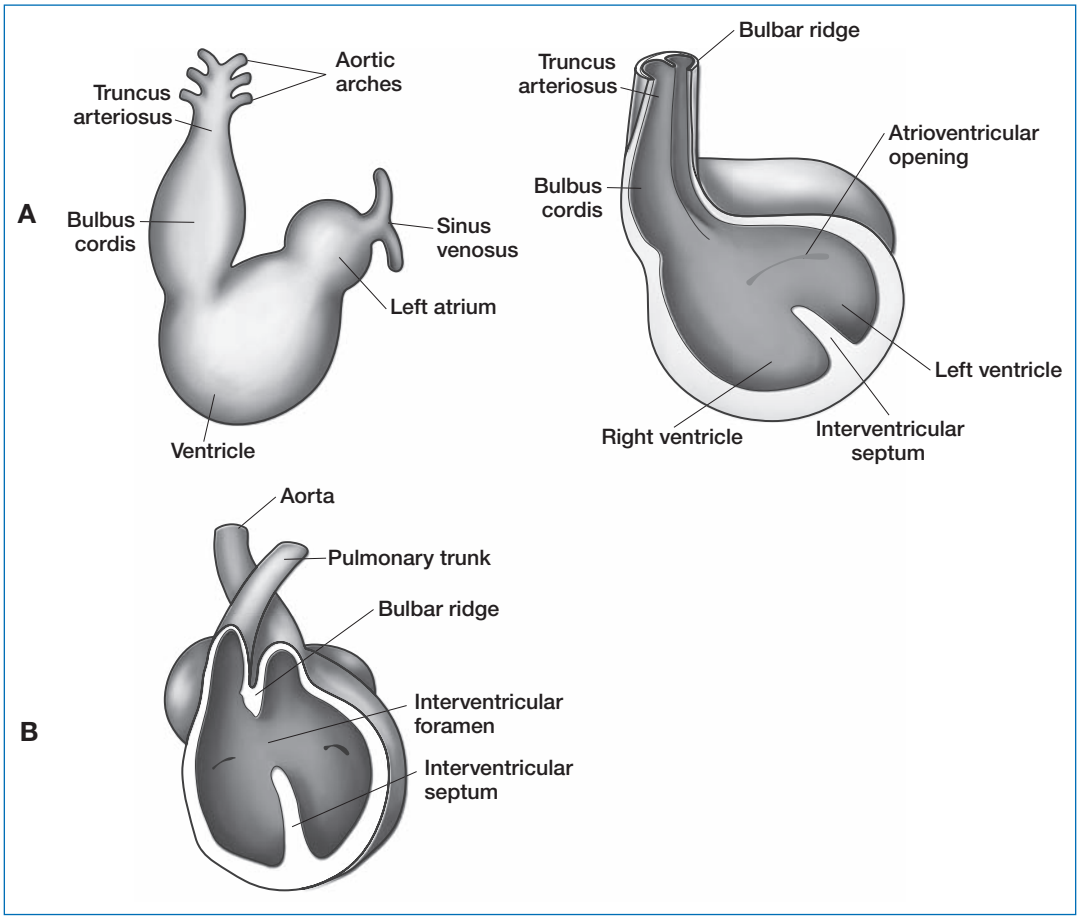


FIGURE 1.12 Partitioning of the ventricles. (A) Five chambers are present in the heart at 5 weeks' gestation. (B) At 6 weeks, the bulbus cordis has been taken into the ventricles and the interventricular septum has partitioned the ventricles into right and left sides.

a continuous circulation from lung to heart. The pulmonary and aortic valves (semilunar valves) develop from dilations within the pulmonary artery and aorta. The ebb-and-flow circulation through these structures causes them to hollow out to form the cusps of the valves. The tricuspid and mitral valves develop from tissue around the atrioventricular canals that thicken and then thin out on the ventricular sides, forming the valves (Figure 1.13; Moore et al., 2015; Sadler, 2015).

Respiratory System

The development of the respiratory system is linked to the development of the face and the digestive system. The respiratory system is composed of the nasal cavities, nasopharynx, oropharynx, larynx, trachea, bronchi, and lungs (Figure 1.14). Development of the lungs occurs in four overlapping stages, which extend from the fifth week of gestation until about 8 years of life. The stages are listed in Table 1.1. At term birth, the normal respiratory system functions immediately. For adequate functioning of the respiratory system, there must be a sufficient number of alveoli, adequate capillary blood flow, and an adequate amount of surfactant produced by the secretory epithelial cells or the type II pneumatocytes. It is the surfactant that prevents alveolar collapse and aids in respiratory gas exchange. Production of surfactant begins around 20 weeks, but does not reach adequate levels until late in gestation. In addition, work to identify the role of epidermal growth factor (EGF) in the development of the fetal respiratory system has determined that EGF indirectly promotes branching morphogenesis of the lung epithelium through a direct effect on the mesenchyme (Moore et al., 2015; Sadler, 2015).

Muscular System

The muscular system develops from mesodermal cells called myoblasts. Striated skeletal muscles are derived from myotomal mesoderm (myotomes) of the somites. The majority of striated skeletal muscle fibers develop in utero. Almost all striated skeletal muscles are formed by 1 year of age. Growth is achieved by an increase in the diameter of the muscle fibers, rather than the growth of new muscle tissue. Smooth muscle fibers arise from the splanchnic mesenchyme surrounding the endoderm of the primitive gut. Smooth muscles lining vessel walls of blood and lymphatic systems arise from somatic mesoderm. As smooth muscle cells differentiate, contractile filaments develop in the cytoplasm, and the external surface is covered by an external lamina. As the smooth muscle fibers develop into sheets or bundles, the muscle cells synthesize and release collagenous, elastic, or reticular fibers (Figure 1.15; Moore et al., 2015; Sadler, 2015).

Cardiac muscle develops from splanchnic mesenchyme from the outside of the endocardial heart tube. Cells from the myoepicardial mantle differentiate into the myocardium. Cardiac muscle fibers develop from differentiation and growth of single cells rather than fusion of cells. Cardiac muscle growth occurs through the formation of new filaments. The Purkinje fibers develop late in

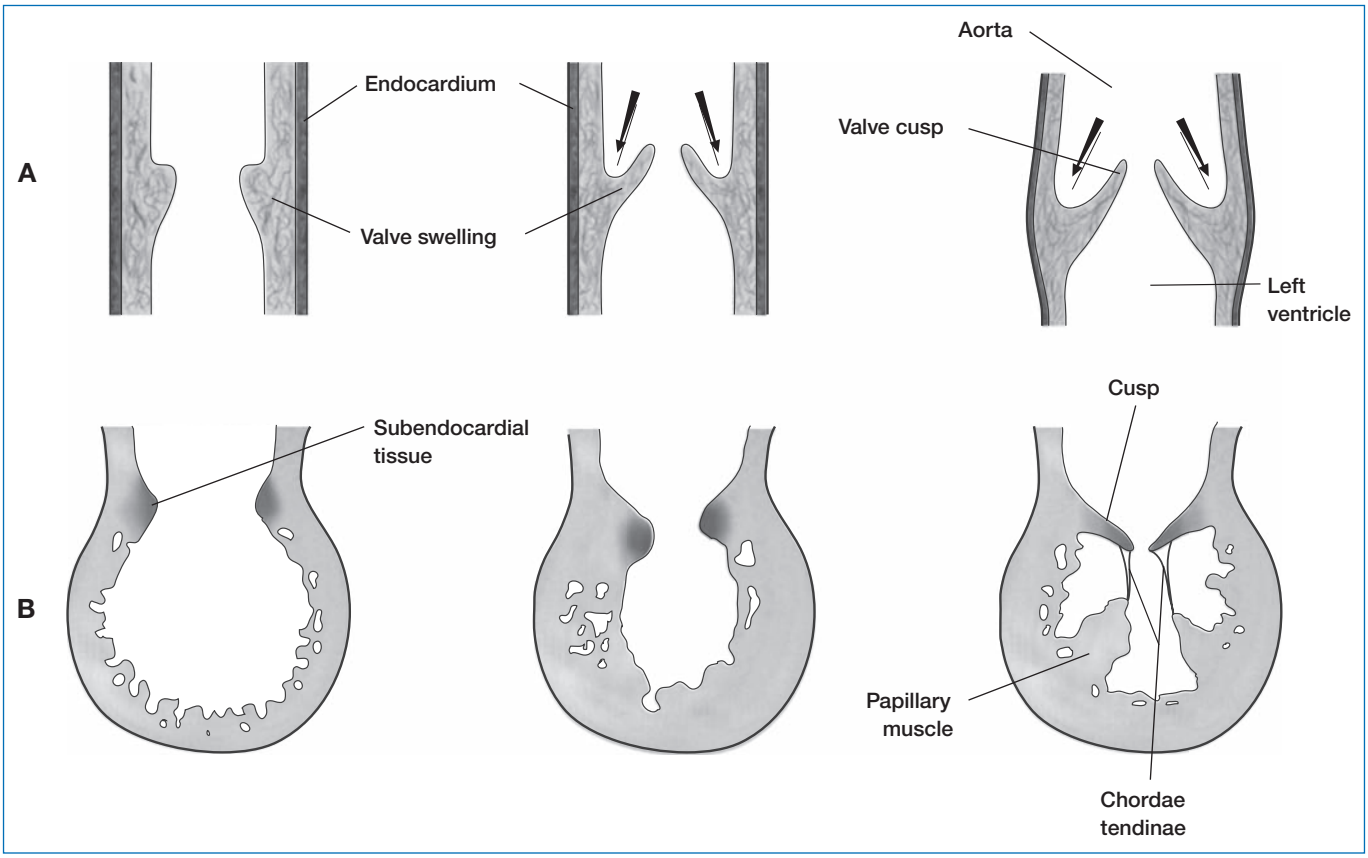


FIGURE 1.13 Formation of the heart valve. (A) Formation of the semilunar valves of the aorta and the pulmonary artery. (B) Formation of the cusps of the atrioventricular valves.

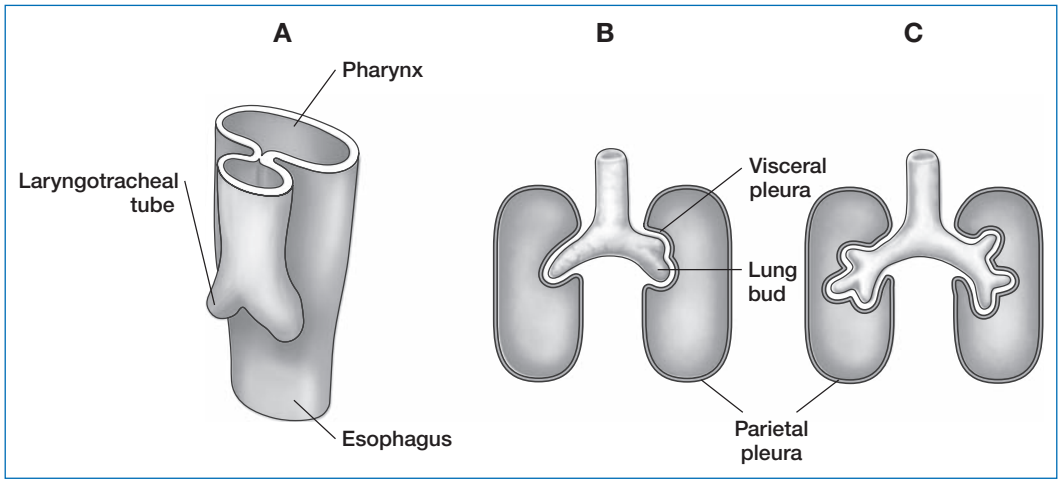


FIGURE 1.14 Development of the pulmonary system. (A) The laryngotracheal groove and tube have formed; the margins of the laryngotracheal groove fuse, forming the laryngotracheal tube. (B) Invagination of the lung buds into the intraembryonic cavity. (C) Division of the lung buds into the right and left mainstem bronchi.

the embryonic period. These fibers are larger and have fewer myofibrils than other cardiac muscle cells. The Purkinje fibers function in the electrical conduction system of the heart (Moore et al., 2015; Sadler, 2015).

Skeletal System

The skeletal system develops from mesenchymal cells. In the long bones, condensed mesenchyme forms hyaline cartilage models of bones. By the end of the embryonic period, ossification centers appear, and these bones ossify by endochondral ossification. Other bones, such as the skull bones, are ossified by membranous ossification in which the mesenchyme cells become osteoblasts (Figure 1.16).

The vertebral column and the ribs arise from the sclerotome compartments of the somites. The spinal column is formed by the fusion of a condensation of the cranial half of one pair of sclerotomes with the caudal half of the next pair of sclerotomes.

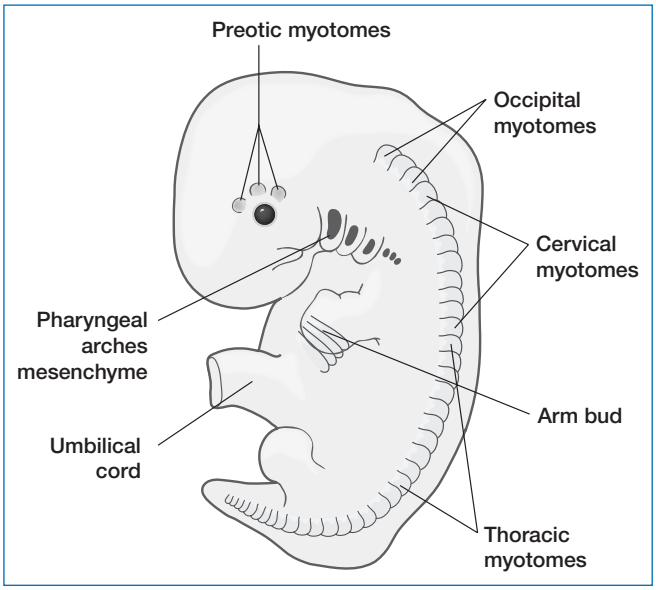


FIGURE 1.15 Origin of the muscles of the head and neck.

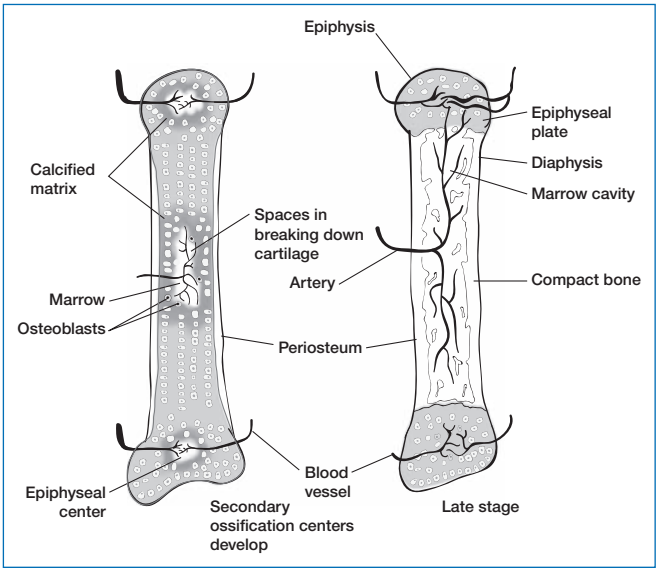


FIGURE 1.16 Endochondral ossification of bones.

TABLE 1.1

STAGES OF LUNG DEVELOPMENT

Stage	Critical Events
Stage 1: Pseudoglandular period: weeks 5–7	Development of the conducting airway
Stage 2: Canalicular period: weeks 13–25	Enlargement of the bronchial lumina and terminal bronchioles Vascularization of lung tissue Development of respiratory bronchioles and alveolar ducts Development of a limited number of primitive alveoli
Stage 3: Terminal sac period: week 24 to birth	Development of primitive pulmonary alveoli from alveolar ducts Increased vascularity Type II pneumatocytes begin to produce surfactant by about 24 weeks
Stage 4: Alveolar period: late fetal period until about 8 years of age	Pulmonary alveoli formed by thinning of terminal air sac lining One-eighth to one-sixth of adult number of alveoli present at term birth Alveoli increase in number until age 8 years

The skull can be divided into the neurocranium and the viscerocranium. The neurocranium forms the protective covering around the brain. The viscerocranium forms the skeleton of the face. The neurocranium is made up of the flat bones that surround the brain and the cartilaginous structure, or chondrocranium, that forms the bones of the base of the skull. The neurocranium (chondrocranium) is made up of a number of separate cartilages, which fuse and ossify by endochondral ossification to form the base of the skull (Moore et al., 2015; Sadler, 2015).

Gastrointestinal System

The gastrointestinal system is primarily derived from the lining of the roof of the yolk sac. The primitive gut, consisting of the foregut, midgut, and hindgut, is formed during the fourth gestational week (Figure 1.17). The structures that arise from the foregut include the pharynx, esophagus, stomach, liver, pancreas, gallbladder, and part of the duodenum. The esophagus and trachea have a common origin, the laryngotracheal diverticulum. A septum, formed by the growing tracheoesophageal folds, divides the cranial part of the foregut into the laryngotracheal tube and the esophagus. Smooth muscle develops from the splanchnic mesenchyme that surrounds the esophagus. The epithelial lining of the esophagus, derived from the endoderm, proliferates, partially obliterating the esophageal lumen. The esophagus undergoes recanalization by the end of the embryonic period (Moore et al., 2015; Sadler, 2015).

The stomach originates as a dilation of the caudal portion of the foregut. The characteristic greater curvature of the stomach develops because the dorsal border grows faster than the ventral border. As the stomach develops further, it rotates in a clockwise direction around the longitudinal axis. The duodenum is derived from the caudal and cranial portions of the foregut and the cranial portion of the midgut. The junction of the foregut and midgut portions of the duodenum is normally distal to the common bile duct (Moore et al., 2015; Sadler, 2015).

The liver, gallbladder, and biliary ducts originate as a bud from the caudal end of the foregut. The liver is formed by growth of the hepatic diverticulum, which grows between the layers of the ventral mesentery, forming two parts. The liver forms from the largest cranial portion. Hepatic cells originate from the hepatic diverticulum. Hematopoietic tissue and Kupffer cells are derived from the splanchnic mesenchyme of the septum transversum. The liver develops rapidly and fills the abdominal cavity. The liver begins

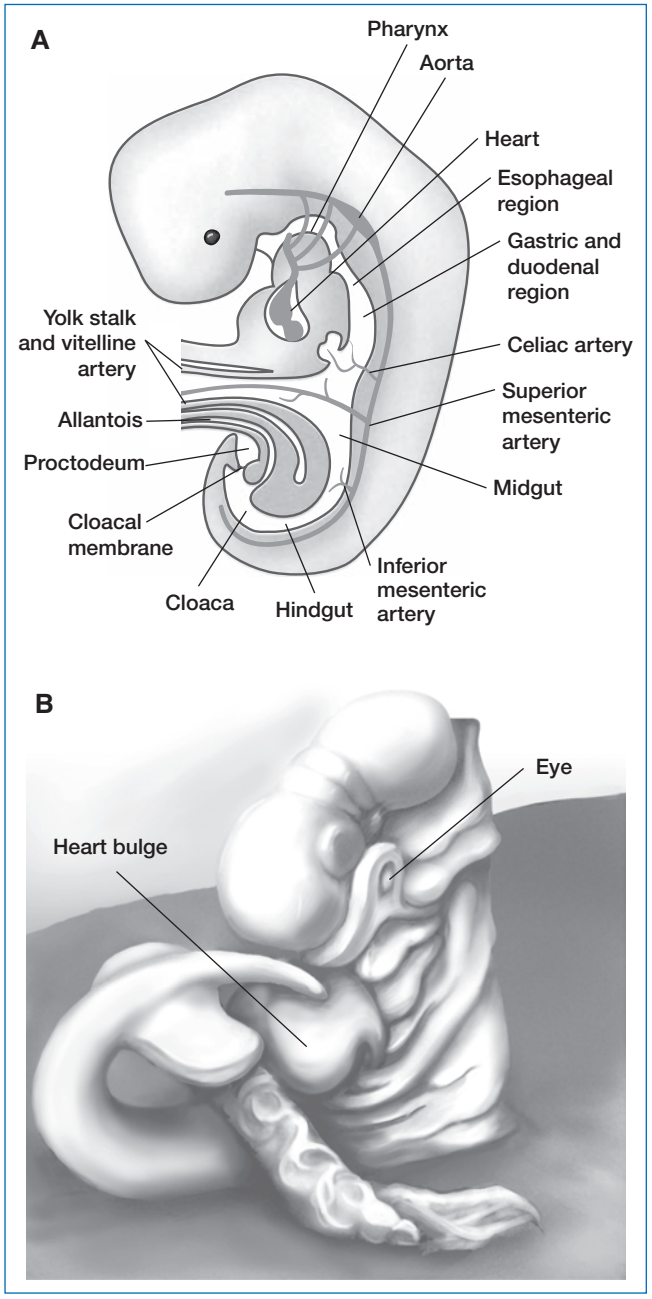


FIGURE 1.17 (A, B) The primitive gut. The early gastrointestinal system presents in an embryo at about 4 weeks' gestation.

its hematopoietic function by the sixth gestational week (Moore et al., 2015; Sadler, 2015).

The smaller portion of the hepatic diverticulum forms the gallbladder. The common bile duct is formed from the stalk connecting the hepatic and cystic ducts to the duodenum. By the 12th week, bile formation begins by the hepatic cells. The pancreas is derived from the pancreatic buds that arise from the caudal part of the foregut. Insulin secretion begins at week 10 (Moore et al., 2015; Sadler, 2015).

The structures that are derived from the midgut include the remainder of the duodenum, the cecum, the appendix, the ascending colon, and the majority of the transverse colon. The intestines undergo extensive growth during the first weeks of development. The liver and kidneys occupy the abdominal cavity, restricting the space available for intestinal growth. The growth of the intestines is accommodated through a migration out of the abdominal cavity via the umbilical cord. A series of rotations occurs before the intestines return to the abdomen. The first rotation is counterclockwise, around the axis of the superior mesenteric artery. At about the 10th week, the intestines return to the abdomen, undergoing further rotation. When the colon returns to the abdomen, the cecal end rotates to the right side, entering the lower right quadrant of the abdomen. The cecum and appendix arise from the cecal diverticulum, a pouch that appears in the fifth week of gestation on the caudal limb of the midgut loop (Figure 1.18; Moore et al., 2015; Sadler, 2015).

The hindgut is that portion of the intestines from the midgut to the cloacal membrane. The latter structure consists of the endoderm of the cloaca and the ectoderm of the anal pit. The cloaca is divided by the urorectal septum. As the septum grows toward the cloacal membrane, folds from the lateral walls of the cloaca grow together, dividing the cloaca into the rectum and upper anal canal dorsally and the urogenital sinus ventrally. By the end of the sixth week, the urorectal septum fuses with the cloacal membrane, forming a dorsal anal membrane and a larger ventral urogenital membrane. At about the end of the seventh gestational week, these two membranes rupture, forming the anal canal (Moore et al., 2015; Sadler, 2015).

Urogenital System

The development of the urinary and genital systems is closely related. The urogenital system develops from the intermediate mesenchyme, which extends along the dorsal body wall of the embryo. During embryonic folding in the horizontal plane, the intermediate mesoderm is moved forward and is no longer connected to the somites. This mesoderm forms the urogenital ridge on each side of the primitive aorta. Both the urinary and genital systems arise from this urogenital ridge. The area from which the urinary system is derived is called the nephrogenic cord. The genital ridge is the area from which the reproductive system is derived (Moore et al., 2015; Sadler, 2015).

There are three stages of development of the kidney: the pronephros, the mesonephros, and the metanephros. The pronephros, a nonfunctional organ, appears in the first month of gestation and then degenerates, contributing only a duct system for the next developmental stage. The mesonephros uses the duct of the pronephros and develops caudally to the pronephros (Figure 1.19). The mesonephros begins to produce urine during development of the metanephros. The mesonephros degenerates by the end of the embryonic period. Remnants of the mesonephros persist as genital ducts in males or vestigial structures in females. The metanephros appears in the fifth week of gestation and becomes the permanent kidney. The metanephros begins to produce urine by about the 11th week of gestation. The number of glomeruli increases until week 32, when the fetal kidney becomes subdivided into lobes. The urinary bladder and the urethra arise from the urogenital sinus and the splanchnic mesenchyme. The caudal portion of the mesonephric ducts is incorporated into the bladder, giving rise to the ureters (Moore et al., 2015; Sadler, 2015).

Although the genetic sex of the embryo is determined at conception, the early development of the genital system is indistinguishable until the seventh week of gestation. In the seventh week, the gonads begin to differentiate. The ovaries and the testes are derived from the coelomic epithelium, the mesenchyme, and the primordial germ cells. Development of female sexual organs occurs in the absence of hormonal stimulation precipitated by the H-Y antigen gene carried on the Y chromosome. If the Y chromosome is present, testes develop; otherwise, ovaries develop (Moore et al., 2015; Sadler, 2015).

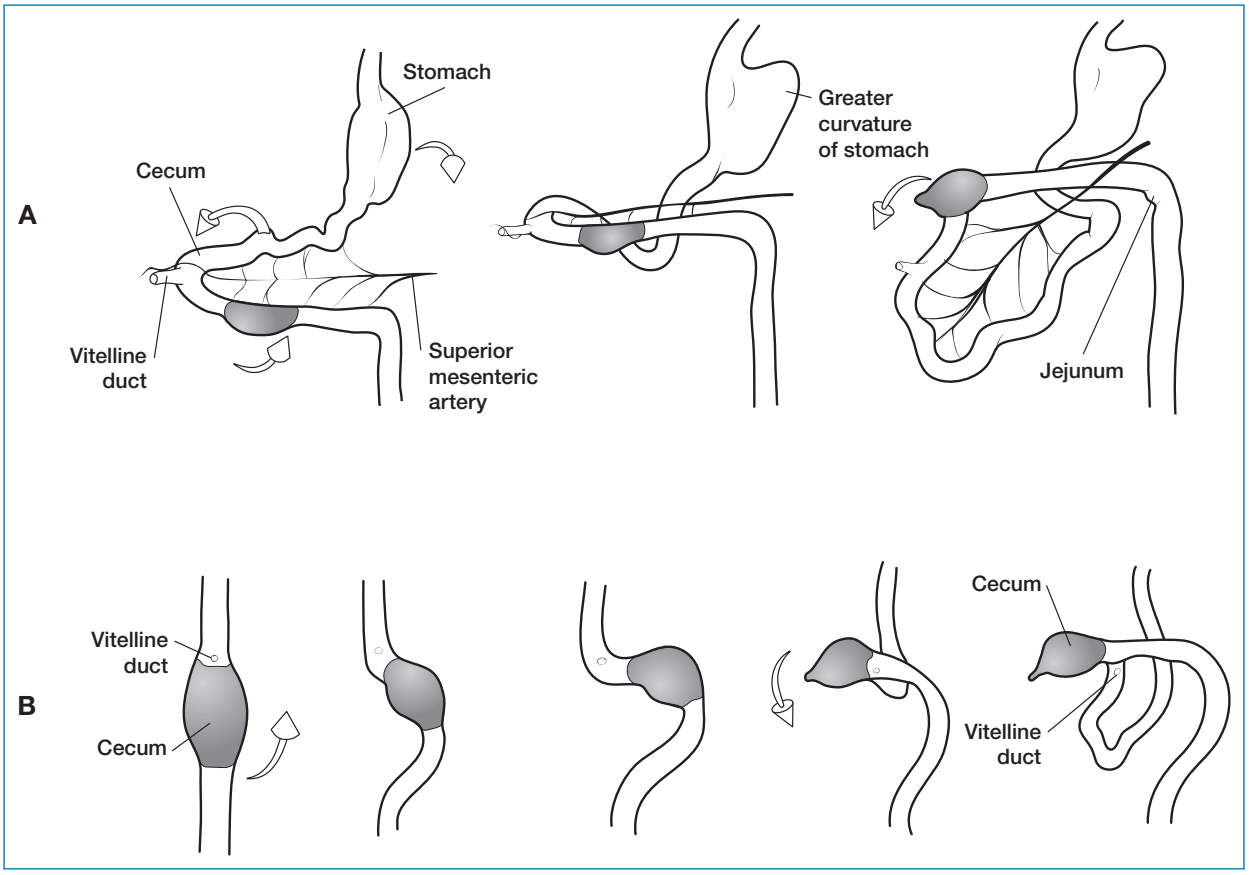


FIGURE 1.18 Migration and rotation of the midgut. (A) Counterclockwise 90° rotation of midgut loop and "herniation" into extraembryonic cavity. (B) Counterclockwise 180° rotation of midgut loop on return to the abdominal cavity.

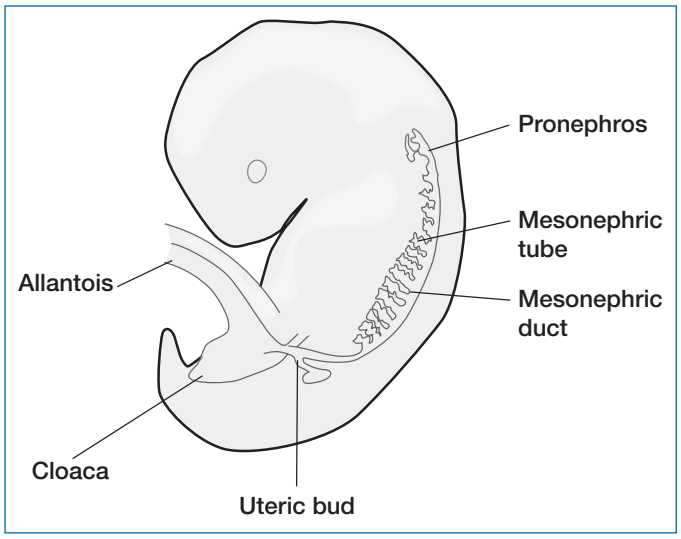


FIGURE 1.19 Development of the kidney. The locations of the pronephros and mesonephros.

FETAL PERIOD: WEEK 9 THROUGH BIRTH

The fetal period begins at the start of week 9 following conception and continues through the duration of pregnancy. It is characterized by further growth and development of the fetus and the organs formed during the embryonic period.

Weeks 9 to 12

At the beginning of this period, the head is large, and the body begins growing faster than the head. The face is broad and characterized by a wide nose and widely spaced eyes. The mouth is formed, and palate formation is complete. Tooth buds appear for the baby teeth. Fingernails are present, and the fetus can curl its fingers to make a fist. The intestines enter the abdomen from the umbilical cord. By the end of the 12th week, blood formation shifts from the liver to the spleen. The fetus can produce urine and excretes it into the amniotic fluid. By the end of the 12th week, the sex of the fetus can be identified by appearance of the external genitalia. By week 12, the fetus weighs 45 g (1.6 oz) and has a C-R length of 8 cm (3.2 inches; Moore et al., 2015).

Weeks 13 to 16

During this time of rapid growth, the fetal head becomes smaller in proportion to the body. The appearance of hair patterning is forming on the head, and *lanugo*, a fine downy hair, is found on the body. Fingerprints are now developed. The fetus can now open its mouth, make a sucking motion, and swallow amniotic fluid. Ossification of the fetal skeleton is active during this time. Reflex response and muscular activity begin. The lower limbs lengthen during this time, and limb movement is more coordinated. In females, the ovaries differentiate and contain primordial follicles. At 16 weeks, the fetal weight is about 200 g (7 oz) and the C-R length is 13.5 cm (5.4 inches; Moore et al., 2015; Sadler, 2015).

Weeks 17 to 20

This marks a period of slower growth. The skin is covered in a fatty, cheese-like substance called *vernix caseosa* that protects it from exposure to amniotic fluid. The limbs are in proportion to the rest of the body and muscles are well developed. Myelination of the spinal cord begins at 20 weeks. Lanugo now covers the body, and brown fat begins to form at the base of the neck, behind the sternum, and around the kidneys. Fetal movement is usually felt by the mother around 18 weeks. The uterus is formed in the female fetus by 18 weeks, and at 20 weeks the testes begin to descend in the male fetus. At 20 weeks, the fetus has a crown to heel (C-H) length of 25 cm (10 inches) and a weight of 435 g (15 oz; Moore et al., 2015; Sadler, 2015).

Weeks 21 to 25

During this period, there is substantial weight gain, but the fetus is thin and has little subcutaneous fat. The skin is wrinkled and translucent red because the capillaries are close to the surface of the skin. The fetus has a grasp, and startle reflex and rapid eye movements begin. Eyebrows and eyelashes are fully formed. Teeth that will become second molars are forming. At 24 weeks, the lungs begin to produce surfactant. IgG levels reach maternal levels. At 24 weeks, the fetus has a C-H length of 28 cm (11.2 inches) and a weight of 780 g (1 lb 11½ oz; Moore et al., 2015; Sadler, 2015).

Weeks 26 to 29

The fetal lungs, pulmonary capillaries, and CNS are more mature, and the fetus is likely to survive if born after 24 to 25 weeks. Blood formation (erythrocyte production) shifts from the spleen to the bone marrow. The CNS is now mature enough to direct breathing movements and control body temperature. There is now enough subcutaneous fat to help maintain body temperature. The eyelids that have been closed since 9 weeks' gestation start to open. In males, the testes descend into the inguinal canal and upper scrotum. At 28 weeks, the fetus has a C-H length of 35 cm (14 inches) and a weight of 1,200 to 1,250 g (2 lb 12 oz; Moore et al., 2015; Sadler, 2015).

Weeks 30 to 34

This period marks a rapid increase in body fat and muscle. Bones are fully developed but are soft and pliable. The lungs are not yet mature but developed enough to provide gas exchange if the fetus were to be born during this period. Surfactant production is not quite at mature levels. The fetus exhibits rhythmic breathing movements as a result of a more mature CNS. The pupillary light reflex is present at 30 weeks. The fetal skin is smooth and pigmented, and the fingernails reach the fingertips. At 32 weeks, the fetus has a C-H length of 38 to 43 cm (15.2–17.2 inches) and weighs 2,000 g (4 lb 7 oz; Moore et al., 2015; Sadler, 2015).

Weeks 35 to 36

Growth of all body systems continues until birth but at a slower rate. The circumference of the head and abdomen is approximately equal by 36 weeks. The fetus starts to look "plump" and the skin is less wrinkled. Lanugo is disappearing. In males, the testes are in the scrotum. In both males and females, breasts are enlarged. At 36 weeks, the fetus has a C-H length of 42 to 48 cm (16.8–17.2 inches) and a weight of 2,500 to 2,750 g (5 lb 8 oz to 6 lb 1 oz; Moore et al., 2015; Sadler, 2015).

Weeks 37 to 40

The fetus is considered *full term* between 38 and 40 weeks. During the last few weeks of gestation, the fat increases in the fetus at a rate of 14 g/day; however, white fat makes up 16% of its total weight. Amniotic fluid decreases to 500 mL or less as the fetal mass fills the uterus. The measurement of the fetal foot is slightly larger than the femur and this is used as an alternate measurement to confirm fetal age. The chest is more prominent but slightly smaller than the diameter of the head. The earlobes are firm, and the skin has a smooth polished appearance. Vernix caseosa is present in the deep folds and creases of the skin. The lungs are well developed and have the ability to exchange gases. The lecithin-sphingomyelin (L/S) ratio is approaching 2:1, indicating lung maturity. At term, the fetus weighs 3,200 g or more and is 48 to 52 cm (19–21 inches) long (Moore et al., 2015; Sadler, 2015).

DEVELOPMENTAL RISKS

The fetus is at less risk for structural defects caused by teratogenic factors than is the embryo; however, there is still a risk for functional impairment of existing structures. This risk is addressed in the section on environmental factors. Changes in specific organs or organ systems during the fetal period are discussed in the section on the development of specific organs (Moore et al., 2015; Sadler, 2015). For a summary of prenatal development, see Box 1.2.

Congenital Defects

Congenital defects or anomalies are structural or anatomic abnormalities present at birth. Congenital defects vary in severity and location, ranging from minor insignificant defects to major organ system defects and are attributed to genetic or chromosomal abnormalities or to maternal or environmental factors. Most congenital defects result from an interaction between genetic and environmental factors, or multifactorial inheritance. Congenital defects caused by single-gene disorders and chromosomal abnormalities are discussed in Chapter 40, Human Genetics and Genomics: Impact on Neonatal Care. The influence of the environment on embryonic development is discussed in this section.

Box 1.2

THREE PERIODS OF FETAL DEVELOPMENT

Embryonic Period

Extends from the fertilization of the ovum

Period 1: Preembryonic Period

Extends from the fertilization of the ovum to the formation of the embryonic disk with three germ layers—weeks 1 to 3.

Period 2: Embryonic Period

Period of rapid growth and differentiation; formation of major organ systems occurs—weeks 4 to 8.

Period 3: Fetal Period

Further growth and development of organ systems—extends from weeks 9 to 40 (term).

Source: Data from Moore, K. L., & Persaud, T. V. N. (2008). *The developing human: Clinically oriented embryology* (8th ed.). Philadelphia, PA: Saunders.

Moore and Persaud (2008) listed six mechanisms that can cause congenital defects: (1) too little growth, (2) too little resorption, (3) too much resorption, (4) resorption in the wrong location, (5) normal growth in an abnormal position, and (6) overgrowth of a tissue or structure. Embryonic organs are most sensitive to noxious agents during a period of rapid cell growth and differentiation. Damage to the primitive streak at about 15 days of gestation could cause severe congenital malformations of the embryo because of its role in the production of intraembryonic mesoderm, from which all connective tissue is formed. Biochemical differentiation occurs before morphologic differentiation, so organs or structures are sensitive to the action of teratogens before they can be identified.

Critical Periods of Human Development

Environmental influences during the first 2 weeks after conception may prevent successful implantation of the blastocyst and cause spontaneous abortion of the embryo. The most sensitive period for the embryo, known as the *critical period*, is the period of organogenesis, during the first 8 weeks of development. Each organ has a critical period during which its development is most likely to be adversely affected by the presence of teratogenic agents; however, some organs such as the brain are sensitive throughout fetal development (Moore et al., 2015).

The terms *congenital anomaly*, *congenital malformation*, and *birth defect* are used synonymously to describe structural abnormalities in an infant; however, according to Moore and Persaud (2008), there are four classifications of congenital anomalies: malformation, disruption, deformation, and dysplasia. A malformation is a structural defect of an organ or larger body region. Usually a malformation is a defect of a morphogenic or developmental field and may result in complex or multiple malformations. A disruption is an interruption of a normal developmental process. This may be caused by a teratogen such as a drug or virus; however, it is not inherited. A deformation is an alteration in form or shape that results from mechanical forces in otherwise healthy tissue. Dysplasia is abnormal development of tissue and may affect several organs.

Birth defects are a leading cause of infant death, accounting for more than 20% of all infant deaths. The generally reported incidence of congenital defects is about 2% to 3%. The actual incidence is higher because some defects are not apparent at birth. Close to 12% of birth defects are not discovered until after the newborn period. The incidence of all defects (including both minor and major defects) is approximately 14% (Lewis, 2009; Moore et al., 2015; Sadler, 2015).

Environmental Factors

Environmental factors cause 7% to 10% of congenital anomalies. During the critical period, or the first 8 weeks, when cell division, cell differentiation, and morphogenesis take place, the fetal structures are most sensitive to environmental agents known as *teratogens*. Each organ or structure has its own critical period in which exposure to teratogens can cause malformations of functional disturbances in varying severity depending on the timing and the teratogen. Teratogens are agents such as chemicals, viruses, radiation, drugs, maternal disease, and other environmental factors that cause birth defects (Lewis, 2009; Moore et al., 2015).

Infectious Agents

Several viral agents including rubella, cytomegalovirus (CMV), herpes simplex virus (HSV), and HIV have been positively identified as teratogenic to the developing fetus. Rubella (German measles) is a viral infection spread through the air or by close contact. The virus can cross the placenta, and during the first trimester can cause cataracts, permanent hearing loss, cardiac malformations (especially patent ductus arteriosus and pulmonary stenosis), and congenital rubella syndrome in the fetus. If exposed in the second or third trimester, the fetus can develop learning disabilities or speech and hearing problems. Prevention is the goal; however, women should be tested to determine if the rubella antibody is present; if not, they should be vaccinated as long as they are not pregnant and will avoid pregnancy for at least 6 months.

CMV is a virus belonging to the herpes family. It is transmitted by direct contact of body fluids including urine, saliva, blood, semen, and breast milk. Approximately 30% to 50% of women have never been infected with CMV, and infected women have no symptoms (Sadler, 2015). One in 200 infants is CMV infected, but only one in five will become ill (Centers for Disease Control and Prevention [CDC], n.d.-a). If exposed in early gestation, the embryo will likely spontaneously abort. A small number of infants who are infected will have microcephaly, meningoencephalitis, hearing and vision loss, mental retardation, and/or seizures (CDC, n.d.-a).

HSV is one of the most common sexually transmitted infections among adult women and is transmitted across broken skin and mucous membrane by direct exposure to the virus. If a woman has a primary outbreak during late pregnancy, there is a 30% to 50% risk of transmission to the fetus. Infection to the fetus is transmitted during birth 85% of the time. An infected fetus has a mortality rate of 50%. Infants who survive may have significant neurologic defects, blindness, and seizures (Moore et al., 2015; Sadler, 2015).

HIV is the virus that causes AIDS. HIV is transmitted through body fluids—blood, semen, genital fluids, and human milk—and can cross the placenta in pregnancy. Almost all pediatric cases of HIV are acquired in utero or through breastfeeding. Women who are treated in pregnancy with an antiretroviral medication reduce the risk of transmission to 2% (Peterson, 2019). Anomalies associated with HIV are microcephaly, growth factor, and craniofacial features.

Toxoplasmosis is caused by a protozoan, *Toxoplasma gondii*, and when exposed in utero can cause hydrocephalus, cerebral calcification, microphthalmia, and ocular defects in the fetus. *T. gondii* can be contracted from raw or undercooked meat, by handling feces of infected cats, or from the soil. The risk and severity depend on the timing of the exposure in pregnancy (Moore et al., 2015; Sadler, 2015).

Untreated primary maternal infections of *Treponema pallidum*, the spirochete that causes syphilis, can result in serious congenital anomalies or stillborn infants. Congenital syphilis is classified as early or late. Early congenital syphilis is defined as in the first 3 months of life and may cause vesiculobullous lesions, rash, lymphadenopathy, hepatosplenomegaly, and a mucopurulent nasal discharge known as "snuffles." Late congenital syphilis occurs around or after age 2 and includes symptoms such as gummatous ulcers on the nose, septum, and palate, bossing of frontal and parietal bones, optic atrophy leading to blindness, interstitial keratitis, and sensorineural deafness. Treatment must be as early as possible to prevent complications and transmission of the infection to the fetus (Moore et al., 2015).

Zika virus is a growing public health problem. When a fetus is exposed to Zika, resultant malformations may occur. The most common effects are microcephaly, macular scarring and retinal changes, contractures, clubfoot, arthrogryposis, and hypertonia (CDC, n.d.-c). For more information on Zika, please see Chapter 26, Emerging Infections.

Other viral agents have been implicated as causes of congenital malformations. Such malformations have been reported following

maternal infection with mumps, varicella, echovirus, coxsackie virus, and influenza virus. The incidence of congenital malformations following these infections is unknown, but is suspected to be low (Sadler, 2015). (For further information on viral agents, see Chapter 11, Immune System).

Drugs/Medications

Drug safety is a primary concern during pregnancy, especially in women with pregestational disease. Safety of a medication cannot be tested on pregnant women for obvious ethical reasons as it could expose a fetus to possible teratogens.

Few drugs are known to be teratogenic; however, no drug can be considered completely safe. The U. S. Food and Drug Administration (FDA) as of June 2015 established three labels for prescription drugs used in pregnancy or preconception. They are 8.1 Pregnancy (including during labor); 8.2 Lactation; and 8.3 Females and Males of Reproductive Potential (FDA, 2014). Over-the-counter medications are not included in this labeling nomenclature (FDA, 2014). The FDA established a pregnancy exposure registry to maintain up-to-date information on the medication along with a risk summary (FDA, 2014).

Drugs that are known teratogens that can cause birth defects include antibiotics streptomycin and tetracycline; antineoplastic agents; anticoagulants, anticonvulsants; hormones such as adrenocorticoids and diethylstilbestrol (DES); antithyroid drugs; psychotropics; anti-anxiety agents such as diazepam; and retinoic acid (a metabolite of vitamin A).

Hormonal agents are also implicated in the incidence of congenital defects. Androgenic agents (progestins) may cause masculinization of female fetuses. DES, a synthetic estrogen used to prevent abortion in the 1940s and 1950s, has been found to cause an increased incidence of vaginal and cervical cancer in female children exposed to the drug in utero. There are also associated abnormalities of the reproductive system, often causing reproductive dysfunction (Moore et al., 2015; Sadler, 2015).

Amphetamines are associated with oral clefts and heart defects. Salicylates (aspirin), a commonly used medication during pregnancy, may be harmful to the fetus if taken in large amounts or may lead to bleeding problems. Isotretinoin, a drug used to treat acne, causes craniofacial abnormalities, cleft palate, thymic aplasia defects, and neural tube defects (Sadler, 2015).

Opioids, often prescribed for pain relief, if used in pregnancy can result in a premature birth, intrauterine growth restriction (IUGR), and the infant may experience withdrawal, referred to as neonatal abstinence syndrome (NAS; March of Dimes, n.d.). NAS secondary to in utero opioid exposure increased fivefold in the United States from 2000 to 2012, and has continued to rise with recent rates reported as high as 20 per 1,000 live births (Milliren et al., 2018). For more information on NAS, please see Chapter 30, Neonatal Abstinence Syndrome.

Illicit Drugs

Social or recreational drugs are highly suspected of contributing to congenital defects and the risk of spontaneous abortion. Drugs such as lysergic acid diethylamide (LSD) have been associated with limb abnormalities and CNS abnormalities. Other drugs that may be teratogenic include phencyclidine and marijuana. "Crack" cocaine has been associated with preterm birth (PTB), low birth weight (LBW), premature rupture of membranes (PROMs), placental abruption, and sudden infant death syndrome (SIDS; Gouin, Murphy, & Shah 2011). The tendency of drug abusers to use multiple drugs, combined with poor nutritional habits and lack of prenatal care, makes it difficult to establish the effects of the drugs individually.

Marijuana. Cannabis (marijuana, hashish, or sensimilla, all products of the *Cannabis sativa* or *Cannabis indica* plant) is the most commonly used psychoactive substance in the United States with an estimated 1 in 5 adults aged 18 to 25 years reporting use in the past month in 2015 (Center for Behavioral Health). Recent estimates of the prevalence of cannabis use among pregnant women in the United States range between 3% and 16%, and the National Survey on Drug Use and Health suggests that cannabis use among pregnant women in the United States has increased as much as 62% between 2002 and 2014 (Brown et al., 2017).

As yet, no teratogenic effects of marijuana have been reported; yet, research on the teratogenicity of marijuana is difficult since it remains illegal in many states. Co-use of other substances is common among prenatal and postpartum marijuana users.

Evidence is inconclusive as to its effect on premature birth or low birth weight; however, there is evidence to suggest a potential impact on fetal brain development (National Institute on Drug Abuse, 2018). Ko et al. (2018) found that prenatal marijuana use was not independently associated with lower average birthweight or gestational age; however, postpartum marijuana use was associated with depressive symptoms and shorter breastfeeding duration. Growing evidence suggests prenatal cannabis exposure has a detrimental impact on offspring neurocognitive function starting in the toddler years (Wu, Jew, & Lu, 2011). More research is needed especially as marijuana becomes legal in many states.

Alcohol. The term *fetal alcohol syndrome* (FAS) is used to describe the cluster of defects characteristic of maternal ingestion of alcohol. A major factor in the development of FAS is timing, amount, and frequency of alcohol consumption during pregnancy. Infants with FAS may exhibit craniofacial abnormalities, microcephaly, limb deformities, smooth philtrum, thin upper lip, small palpebral fissures, and short nose. They may have visual impairment. They may exhibit cognitive impairment; impaired fine motor skills; developmental disabilities; attention deficit disorder; and seizure disorder as well as alcohol-related birth defects (ARBD) such as heart and kidney defects, malformations of the bone, and hearing (CDC, n.d.-b). Fetal alcohol spectrum disorder (FASD) is a modern term that describes the range of permanent effects of alcohol use in pregnancy. This cluster of conditions is preventable if pregnant women do not consume alcohol (CDC, n.d.-b). There is no known safe level of alcohol consumption during pregnancy, and even low levels of prenatal alcohol exposure have been found to cause adverse fetal effects, and not just in the brain (Sarman, 2018)

Tobacco. The dangers of smoking cigarettes in pregnancy have been well documented. Use of tobacco during pregnancy can lead to PTB, LBW, PROMs, placenta previa, placental abruption, or stillbirth. The fetus can suffer from growth restriction because of the vasoconstrictive properties of nicotine, which decreases oxygenated blood to the fetus. Damage to fetal lung and brain tissue is also possible (CDC, n.d.-f). Katoka et al. (2018) demonstrated that newborn weight decreased as the category of number of cigarettes per day increased, with a significant reduction at the 6 to 10 cigarettes. Based on the study results and the principle of harm reduction, if a pregnant woman is unable to quit smoking, she should be encouraged to reduce consumption to less than six cigarettes per day.

E-Cigarettes. Electronic nicotine delivery systems (ENDS), a comparatively new phenomenon, are gaining in popularity, especially among adolescent nonsmokers, and are frequently perceived as being safer than regular cigarettes (Dutra & Glantz, 2014; Grana, Benowitz, & Glantz, 2014). Because ENDS emissions have been found to have lower levels and overall numbers of toxins compared with tobacco cigarettes, they are

commonly marketed as safer alternatives without regard to the intrinsic adverse effects of nicotine (Grana et al., 2014). If pregnant women perceive ENDS as safer than tobacco cigarettes, there is potential for unrealized harm because current tobacco-smoking pregnant women may use ENDS to decrease the amount of tobacco cigarettes smoked during pregnancy (England, Tong, Klobitz, Kish-Doto, & Southwell, 2016; Wigginton, Gartner, & Rowlands, 2017). This perceived harm reduction strategy could result in continued nicotine exposure and associated complications, as well as currently undetermined additional maternal–fetal risks (Bhandari et al., 2018). The variety of flavorings offered may also put the fetus at risk for damage to the lungs and brain (CDC, n.d.-d). Another potential ENDS-associated issue important to expecting mothers is the possibility of unintentional ingestion of ENDS liquids by young children at home (American Association of Poison Control Centers, n.d.). In addition to the perception of lower health risks, the relative lesser cost of e-cigarettes compared with tobacco cigarettes could encourage their use. As such, for women who already smoke and are facing financial hardship during pregnancy, e-cigarettes may seem like a rational solution.

Ionizing Radiation. There is no established "safe" level for radiation. Large amounts of exposure during pregnancy can be detrimental to the fetus; however, this is a rare occurrence. The severity of radiation-induced defects depends on the duration and timing of exposure. Radiation exposure during the first trimester of pregnancy most likely will result in loss of the embryo. High levels of radiation can cause microcephaly, microphthalmia, growth restriction, skeletal and visceral abnormalities, retinal changes, cataracts, and cleft palate. There is no evidence that the small amount of radiation required for modern radiographic studies is harmful; however, caution is used to minimize the exposure to the fetus because of the potential for cumulative effects of radiation exposure throughout the life span (Groen, Bae, & Lim, 2012). Low-dose ionizing radiation (LDIR) is known to promote oxidative stress; however, these levels may not be large enough to result in genomic mutations. There is emerging evidence that oxidative stress causes epigenetic modifications, which can result in permanent cellular transformations without altering the underlying DNA nucleotide sequence. Intrauterine fetal development is highly susceptible to oxidative stress-induced epigenetic programing when exposed to LDIR during pregnancy (Tharmalingam, Sreetharan, Kulesza, Boreham, & Tai, 2017).

Heavy Metals. **Heavy metals such as lead (Pb), cadmium (Cd), cobalt, manganese (Mn), and mercury (Hg) during** pregnancy **put the developing fetal brain at risk (CDC, n.d.-e). More specifically,** high maternal second trimester blood levels of Pb and Mn during **pregnancy** are associated with neural tube defects (NTDs) in the newborn (Özel et al., 2018). Ingestion of predatory fish such as shark, swordfish, king mackerel, and tilefish while pregnant may damage the developing fetal brain and CNS (Mayo Clinic, 2016).

Bisphenol-A. Bisphenol-A (BPA) is an organic compound used to make polycarbonate plastic, epoxy resins, and dental sealants. BPA can be found in plastic baby bottles, plastic lining in canned foods, and polycarbonate plastic containers. The chemical structure of BPA is similar to estrogen and may have the same effect on the body. High levels of BPA found in blood have been associated with recurrent miscarriages, preeclampsia, IUGR, and PTB. Fetal exposure to BPA may result in the development of diabetes or heart disease when the child is older (Endocrine Society, 2015).

Maternal Disease

Pregestational maternal disease can be teratogenic to a fetus. Women with poorly controlled pregestational diabetes have a three to four times higher risk of having a fetus with a birth defect than women in the general population. Anomalies typically occur between weeks 5 and 8 and can include brain anomalies, skeletal defects, developmental abnormalities, and congenital heart defects.

Thyroid deficiency during the last two trimesters of pregnancy and first months after birth can result in mental retardation or other neurologic deficits in the neonate. Hypothyroidism or hyperthyroidism during pregnancy can have an adverse effect on fetal growth and result in neonatal hypothyroidism or hyperthyroidism.

Women with phenylalanine hydroxylase deficiency (phenylketonuria [PKU]) and hyperphenylalaninemia are at risk of having a fetus with congenital anomalies if the phenylalanine levels are elevated in pregnancy. High maternal levels of phenylalanine during pregnancy can result in microcephaly, delayed speech, mental retardation, neurologic damage, congenital heart defects, facial anomalies, microcephaly, and delayed development (Mayo Clinic, 2018).

Other

Another teratogenic factor is hyperthermia caused by maternal use of hot tubs or saunas or by maternal febrile illness during pregnancy. Hyperthermia can increase the incidence of embryonic resorption and malformations. The type and severity of congenital defect depend on the amount of temperature elevation, duration of the exposure, and stage of embryonic development. If the mother is exposed during the critical period (the first 8 weeks) when the CNS is particularly vulnerable to hyperthermia, congenital defects of the CNS may occur (Tobah, 2019).

Good nutrition has long been considered essential for proper growth and development of the fetus. Dietary habits have a profound effect on pregnancy outcomes. However, with the exception of folic acid, in which there is evidence that deficiencies are causally related to defects of the neural tube, there is little known about the role of micronutrients on fetal development. Supplementation of vitamins and minerals must occur within the appropriate critical period of development to be effective. Finally, advanced paternal age has recently been associated with an increased risk of complex disorders such as autism, schizophrenia, autism spectrum disorder, and achondroplasia (Castle, 2018).

SUMMARY

This chapter has provided an overview of embryologic and fetal development, outlined the critical periods of development, and described the more common congenital defects. Knowledge of embryologic and fetal development is essential as a foundation for understanding the role of environment, genetics, physical, or other factors that may have an impact upon anatomy, physiology, or pathophysiology of the organism. The future health of the individual in large part depends on numerous events that take place during gestation. As knowledge of genetics, development, and human pathophysiology improves, better healthcare technologies may emerge that can significantly reduce morbidity and mortality and improve quality of life.

CASE STUDY

A 19-year-old female at approximately 19 weeks of gestation presents to the high-risk clinic by referral from her primary

obstetrician. She had a morphology scan at her doctor's office at 18 weeks with intracranial calcifications noted as well as probably hyperechogenic bowel. She and her husband had moved to North Carolina from a small town in Mississippi. They had married immediately after graduation from high school and he had joined the Army. They had neither family in the area nor any other social support systems. Her primary obstetrician had forwarded prenatal records that described a 24- to 48-hour viral illness between 16 and 17 weeks with a fever of 102°F and flu-like symptoms including myalgia and malaise. Detailed ultrasounds demonstrated numerous intracranial calcifications, microcephaly, pleural effusions, and decreased amniotic fluid. The perinatologist discussed with the couple the probability that she had been exposed to and developed CMV, which was passed on to the fetus. The couple refused amniocentesis following a prolonged discussion with family members in Mississippi because they had decided to continue with the pregnancy regardless of the outcome. The infant was born at 37 weeks and was diagnosed with blindness, deafness, and is likely to have severe mental disabilities.

- How would you explain the CMV infection?
- How would you explain the potential outcomes for the baby as well as the extent of care that would be required for optimal developmental outcome?
- How would you prepare the parents for the care of an infant with multiple serious disabilities?

■ **CMV.** When a woman is infected with CMV for the first time during pregnancy (primary infection), the risk that her baby will get infected is as high as 50%. Primary maternal CMV infections occur in 0.15% to 2.0% of all pregnancies. Infants born with CMV are at risk for long-term disabilities such as mental retardation, learning disabilities, epilepsy, cerebral palsy, hearing impairment or deafness, and visual impairment or blindness. Congenital CMV infection is transmitted to the fetus by maternal viremia and placental infection. Maternal immunoglobulin G (IgG) transports the virus across the placental syncytiotrophoblast. In a primary infection in which the placenta becomes infected with CMV, the ability to provide nutrients and oxygen to the fetus is impaired. The placenta becomes enlarged, and tissue damage occurs due to viral placentitis and revascularization. Many symptoms in the newborn are due to the infection of the placenta rather than the direct effect of the virus on the fetus. A primary CMV infection in the first trimester is associated with the worst outcomes. A maternal infection that occurs prior to conception is unlikely to pass to the fetus.

Although the majority (85%–90%) of congenital infections are asymptomatic, 5% to 20% of infants born to mothers with primary CMV infection are overtly symptomatic. Only 10% to 15% of these babies will show symptoms of infection at birth. Symptoms may include petechia, jaundice, hepatosplenomegaly, microcephaly, IUGR, chorioretinitis, thrombocytopenia, and anemia. Babies born with CMV are also at risk for long-term effects such as sensorineural hearing loss, vision problems, and psychomotor development delay. CMV-infected children have a mortality rate of about 5%, and severe neurologic morbidity occurs in 50% to 60% of survivors. Asymptomatic infants are also at risk of developing long-term neurodevelopmental morbidity, but the risk is much lower than in symptomatic neonates.

Diagnosis is made by viral culture of amniotic fluid and by ultrasound examination. Amniocentesis is essential for prenatal diagnosis and CMV isolation from amniotic fluid is the gold standard for prenatal diagnosis. A high viral load in the amniotic fluid may indicate a poor outcome; however, it may also be related to gestational age at the time of sampling. Once a fetal infection has been diagnosed, the fetus should be closely monitored by ultrasound. Abnormal ultrasound findings include abnormalities in amniotic fluid such as polyhydramnios or oligohydramnios, IUGR, hydrocephaly or microcephaly, intracranial calcifications, cerebral ventriculomegaly or atrophy, hyperechogenic bowel, pseudomeconium ileus, hepatosplenomegaly, ascites or hydrops, and/or necrotic, cystic, or calcified lesions in the brain or liver. Some babies that have been infected with CMV during pregnancy will show signs of problems on ultrasound; however, the absence of sonographic findings does not guarantee a normal outcome. Some fetuses with CMV will not show any signs of infection on ultrasound. Once a fetus is diagnosed with a CMV infection, ultrasounds should be done every 2 to 4 weeks to watch for signs that may predict the outcome. Routine serologic testing is not recommended and should be used only when a pregnant woman develops a flu-like illness or if a CMV infection is suspected following an ultrasound.

Currently, there is no effective therapy for CMV infection, and women can be offered the option of pregnancy termination once a fetal infection is detected by ultrasound or amniocentesis and once a fetus is determined or suspected to be affected. Research on the use of CMV-specific hyperimmune globulin in pregnant women with a primary infection has been reported to improve outcomes; however, further studies are needed. There is also some evidence that ganciclovir treatment of babies with symptoms of congenital CMV may be beneficial for prevention or amelioration of hearing loss.

There are currently no vaccines for CMV and no clinical trials of new vaccines. Prevention of congenital CMV infection by practicing good personal hygiene is crucial. Pregnant women should avoid intimate contact with saliva and urine from young children and use good handwashing after changing diapers and wiping secretions. At least one-third of women in the United States have direct contact with children less than 3 years old. Children and staff who care for children in day-care centers are especially likely to be infected; therefore, pregnant women who have children in day-care settings are especially vulnerable. One should assume that all children under age 3 have CMV in their urine and saliva. Other recommendations include not sharing cups, plates, or toothbrushes, not kissing children on or near the mouth, and not sharing towels or washcloths with a young child.

Reference

Centers for Disease Control and Prevention. (n.d.). Cytomegalovirus (CMV) and congenital CMV infection. Retrieved from https://www.cdc.gov/cmv/congenital-infection.html

ONLINE RESOURCES

Center for Behavioral Health Statistics and Quality. (2016). Key substance use and mental health indicators in the United States: Results from the 2015 National Survey on Drug Use and Health (HHS Publication No. SMA 16-4984, NSDUH Series H-51). Retrieved from https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2015/NSDUH-FFR1-2015/NSDUH-FFR1-2015.htm

Centers for Disease Control and Prevention. (n.d.). Data and statistics on birth defects. Retrieved from https://www.cdc.gov/ncbddd/birthdefects/data.html

Clinical Teratology Web: A project of the TERIS (Teratogen Information System) at University of Washington. Designed to serve as a resource guide for healthcare professionals. Retrieved from http://depts.washington.edu/terisdb/terisweb/index.html

Embryology education. Retrieved from https://embryology.med.unsw.edu.au/embryology/index.php/Main_Page

REFERENCES

American Association of Poison Control Centers. (n.d.). E-cigarettes and liquid nicotine. Retrieved from https://www.aapcc.org/track/ecigarettes-liquid-nicotine

Bhandari, N., Day, K., Payakachat, N., Franks, A., McCain, K., & Ragland, D. (2018). Use and risk perception of electronic nicotine delivery systems and tobacco in pregnancy. *Women's Health Issues, 28*(3), 251–257. doi:10.1016/j.whi.2018.02.005

Brown, Q., Sarvet, A., Shmulewitz, D., Martins, S., Wall, M., & Hasin, D. (2017). Trends in marijuana use among pregnant and nonpregnant reproductive-aged women, 2002–2014. *Journal of the American Medical Association, 317*, 207–209. doi:10.1001/jama.2016.17383

Castel, E. P. (2018). Getting pregnant. How does paternal age affect a baby's health? *Mayo Clinic*. Retrieved from https://www.mayoclinic.org/healthy-lifestyle/getting-pregnant/expert-answers/paternal-age/faq-20057873

Centers for Disease Control and Prevention. (n.d.-a). Babies born with CMV (congenital CMV infection). Retrieved from https://www.cdc.gov/cmv/congenital-infection.html

Centers for Disease Control and Prevention. (n.d.-b). Basics about FASDs. Retrieved from https://www.cdc.gov/ncbddd/fasd/facts.html

Centers for Disease Control and Prevention. (n.d.-c). Congenital Zika syndrome & other birth defects. Retrieved from https://www.cdc.gov/pregnancy/zika/testing-follow-up/zika-syndrome-birth-defects.html

Centers for Disease Control and Prevention. (n.d.-d). E-cigarettes and pregnancy. Retrieved from https://www.cdc.gov/reproductivehealth/maternalinfanthealth/tobaccousepregnancy/e-cigarettes-pregnancy.htm

Centers for Disease Control and Prevention. (n.d.-e). The National Institute for Occupational Safety and Health (NIOSH): Reproductive health and the workplace. Retrieved from https://www.cdc.gov/niosh/topics/repro/heavymetals.html

Centers for Disease Control and Prevention. (n.d.-f). Smoking & tobacco use: Smoking during pregnancy. Retrieved from https://www.cdc.gov/tobacco/basic_information/health_effects/pregnancy/index.htm

Dutra, L. M., & Glantz, S. A. (2014). High international electronic cigarette use among never smoker adolescents. *Journal of Adolescent Health, 55*(5), 595–597. doi:10.1016/j.jadohealth.2014.08.010

Endocrine Society. (2015, January 20). BPA exposure during pregnancy causes oxidative stress in child, mother. *ScienceDaily*. Retrieved from https://www.sciencedaily.com/releases/2015/01/150120142551.htm

England, L., Tong, V., Klobitz, J., Kish-Doto, M., & Southwell, B. (2016). Perceptions of emerging tobacco products and nicotine replacement therapy among pregnant women and women planning a pregnancy. *Preventive Medicine Reports, 4*, 481–485. doi:10.1016/j.pmedr.2016.09.002

Gouin, K., Murphy, K., & Shah, P. S. (2011). Effects of cocaine use during pregnancy on low birth weight and preterm birth: Systemic review and meta-analyses. *American Journal of Obstetrics and Gynecology, 204*, e1–e12. doi:10.1016/j.ajog.2010.11.013

Grana, R., Benowitz, N., & Glantz, S. (2014). E-cigarettes: A scientific review. *Circulation, 129*(19), 1972–1986. doi:10.1161/circulationaha.114.007667

Groen, R. S., Bae, J. Y., & Lim, K. J. (2012). Fear of the unknown: Ionizing radiation exposure during pregnancy. *American Journal of Obstetrics and Gynecology, 206*(6), 456–462. doi:10.1016/j.ajog.2011.12.001

Katoka, M., Carvalheira, A., Ferrari, A., Malta, M., de Barros Leite Carvalhaes, M., de Lima Parada, C., & Malta, M. (2018). Smoking during pregnancy and harm reduction in birth weight: A cross-sectional study. *BMC Pregnancy and Childbirth, 18*(1), 67. doi:10.1186/s12884-018-1694-4

Ko, J., Tong, V., Bombard, J., Hayes, D., Davy, J., & Perham-Hester, K. (2018). Marijuana use during and after pregnancy and association of prenatal use on birth outcomes: A population-based study. *Drug and Alcohol Dependence, 187*, 72–78. doi:10.1016/j.drugalcdep.2018.02.017

Lewis, R. (2009). *Human genetics: Concepts and applications* (9th ed.). New York, NY: McGraw Hill.

March of Dimes. (n.d.). Prescription opioids during pregnancy. Retrieved from https://www.marchofdimes.org/pregnancy/prescription-opioids-during-pregnancy.aspx

Mayo Clinic. (2016). Pregnancy week by week: Pregnancy and fish: What's safe to eat? Retrieved from https://www.mayoclinic.org/healthy-lifestyle/pregnancy-week-by-week/in-depth/pregnancy-and-fish/art-20044185

Mayo Clinic. (2018). Phenylketonuria (PKU). Retrieved from https://www.mayoclinic.org/diseases-conditions/phenylketonuria/symptoms-causes/syc-20376302

Milliren, C. E., Gupta, M., Graham, D. A., Melvin, P., Jorina, M., & Ozonoff, A. (2018). Hospital variation in neonatal abstinence syndrome incidence, treatment modalities, resource use, and costs across pediatric hospitals in the United States, 2013 to 2016. *Hospital Pediatrics, 8*, 15–20. doi:10.1542/hpeds.2017-0077

Moore, K. L., & Persaud, T. V. N. (2008). *The developing human: Clinically oriented embryology* (8th ed.). Philadelphia, PA: Saunders.

Moore, K. L., Persaud, T. V. N., & Torchia, M. G. (2015). *The developing human: Clinically oriented embryology* (10th ed.). Philadelphia, PA: Saunders.

National Institute on Drug Abuse. (2018). Marijuana: Can marijuana use during and after pregnancy harm the baby? Retrieved from https://www.drugabuse.gov/publications/research-reports/marijuana/can-marijuana-use-during-pregnancy-harm-baby

Peterson, A. T. (2019). HIV in pregnancy. In R. M. Ramus (Ed.), *Medscape*. Retrieved from https://emedicine.medscape.com/article/1385488-overview

Özel, Ş., Ozyer, S., Aykut, O., Çinar, M., Yılmaz, O., Caglar, A., & Engin-Ustun, Y. (2018). Maternal second trimester blood levels of selected heavy metals in pregnancies complicated with neural tube defects. *The Journal of Maternal-Fetal and Neonatal Medicine,* 1–7. doi:10.1080/14767058.2018.1441280

Sadler, T. W. (2015). *Langman's medical embryology* (13th ed.). Philadelphia, PA: Lippincott William & Wilkins.

Sarman, I. (2018). Review shows that early foetal alcohol exposure may cause adverse effects even when the mother consumes low levels. *Acta Paediatrica, 107*(6), 938–941. doi:10.1111/apa.14221

Tharmalingam, S., Sreetharan, S., Kulesza, A., Boreham, D., & Tai, T. (2017). Low-dose ionizing radiation exposure, oxidative stress and epigenetic programing of health and disease. *Radiation Research, 188*(4.2), 525–538. doi:10.1667/rr14587.1

Tobah, Y. B. (2019). Pregnancy week by week: Is it safe to use a hot tub during pregnancy? *Mayo Clinic*. Retrieved from https://www.mayoclinic.org/healthy-lifestyle/pregnancy-week-by-week/expert-answers/pregnancy-and-hot-tubs/faq-20057844

U.S. Food and Drug Administration. (2014). *Pregnancy and lactation labeling (drugs) final rule*. Retrieved from https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm

Wigginton, B., Gartner, C., & Rowlands, I. (2017). Is it safe to vape? Analyzing online forums discussing e-cigarette use during pregnancy. *Women's Health Issues, 27*(1), 93–99. doi:10.1016/j.whi.2016.09.008

Wu, C. S., Jew, C. P., & Lu, H. C. (2011). Lasting impacts of prenatal cannabis exposure and the role of endogenous cannabinoids in the developing brain. *Future Neurology, 6*, 459–480. doi:10.2217/fnl.11.27

CHAPTER 2

Prenatal, Intrapartal, and Postpartal Risk Factors

Dolores R. Dzubaty

INTRODUCTION

Women who discover they are pregnant expect to experience an uneventful pregnancy and delivery of a healthy term newborn. Unfortunately, full-term delivery of a healthy newborn is not always the outcome. Women, and their partners, are exposed to a myriad of physical, environmental, psychological, genetic, and behavioral factors that influence pregnancy and the outcome. Even in instances when women have access to excellent prenatal care, there may be unknowing exposure to factors that are detrimental to a fetus. The result may be a pregnancy that is completed preterm and an infant affected by the complications of prematurity, low birth weight (LBW), or possibly congenital disorders. Such outcomes account for increases in neonatal morbidity and mortality. Preterm birth (PTB) and the resultant health complications can affect the newborn throughout the life span. Maternal factors that resulted in poor pregnancy outcomes can also continue to have detrimental effects on the newborn.

Perinatal providers assess and identify patient risk factors that may result in poor pregnancy outcomes. Ideally, education can be provided prenatally so that patients enter the pregnancy in a state of good health, minimizing exposure to known teratogens, and knowledgeable about lifestyle changes that may need to occur. Identification of risk factors and development of education for all women is a global, national, and local concern. Many organizations have contributed to the body of knowledge utilized by healthcare practitioners caring for women before, during, and after pregnancy. This chapter presents information on the risk factors contributing to complications in pregnancy and possible changes that can increase healthy outcomes. The perspective considered will be global as well as national in recognition of the multiple cultures nurses are exposed to in practice.

GLOBAL

Among the eight United Nations Millennium Development Goals (MDG), representatives addressed the needs of all nations in achieving the eradication of poverty, reduction in child mortality, and improvement in maternal health by 2015 (Howson, Kinney, & Lawn, 2012). In October 2015, the United Nations General Assembly adopted the document "Transforming Our World: 2030 Agenda for Sustainable Development" (United Nations [UN], 2015). Within this document, the General Assembly recognized the success and lack of progress toward attainment of the MDG. The Assembly then acknowledged:

> progress has been uneven, particularly in Africa, least developed countries, landlocked developing countries and small island developing States, and some of the Millennium Development Goals remain off-track, in particular those related to maternal, newborn and child health and to reproductive health. We recommit ourselves to the full realization of all the Millennium Development Goals, including the off-track Millennium Development Goals, in particular by providing focused and scaled-up assistance to least developed countries and other countries in special situations, in line with relevant support programmes. The new Agenda builds on the Millennium Development Goals and seeks to complete what they did not achieve, particularly in reaching the most vulnerable. (p. 5)

The Resolution stating the 17 new Sustainable Development Goals (SDG) set forth went into effect January 1, 2016 (UN, 2015, p. 14). The assembly recognized in this document that different nations would have dissimilar challenges in meeting the goals set forth. Implementation of action to reach the SDG and targets would occur on national levels. However, as previously stated, the commitment to maternal, newborn, and child health remains imbedded in these new goals.

NATIONAL

At the national level, member nations have committed to the 2030 Agenda (UN, 2015) and adopted policy, procedure, and support of efforts to improve and sustain the conditions of their own populations. In low-resource countries, there are challenges of infrastructure deficiencies. Fewer healthcare facilities, farther distances to travel to obtain care, and lack of transportation means to obtain care all adversely affect pregnancy outcomes. Cultural practices that are not recognized to support healthy outcomes may still be prevalent in some regions of countries that also have modern services available. The result is disparity in healthcare based on geographic location, adherence to cultural beliefs, and socioeconomic status.

Disparity in healthcare can also be found in more developed countries based on the same factors of geographic location, socioeconomic status, and personal belief system. Healthcare provider

groups such as the Association of Women's Health, Obstetric, and Neonatal Nursing (AWHONN, 2016a) and the Royal College of Nurse Midwives (n.d.) have developed standards of care and educational offerings for nurses and midwives. The purpose is to ensure the delivery of care at all levels to support healthy pregnancy outcomes, reduce prematurity, and provide consistent care. The International Confederation of Midwives (2017) seeks to educate, empower, and provide care to women on a global level. Despite all of the efforts put forth by these groups, healthcare disparity and poor perinatal outcomes persist. The American Academy of Nursing (AAN) Expert Panel on Maternal Infant Health reported that maternal death rates in the United States are rising in African American women but data are not collected consistently across the United States to determine etiologies (Amankwaa et al., 2018).

PERINATAL OUTCOMES INDICATORS

As healthcare delivery differs between countries, common indicators must be chosen to be able to compare improvement or worsening of prenatal outcomes. PTB rate, LBW, and neonatal and infant mortality are three indicators that can be compared.

Preterm Birth

In the United States, PTB and LBW accounted for 25.9% of neonatal deaths and 18% of infant deaths in 2013 according to a report by the March of Dimes (MOD, 2016). The PTB rate as well as the rate of LBW increased in 2016 as reported by the Centers for Disease Control and Prevention (CDC), despite a decrease in the fertility rate. PTB rate, delivery at less than 37 weeks, for all races was 9.85% (Martin, Hamilton, Osterman, Driscoll, & Drake, 2018).

PTBs range from 5% to 18% worldwide with the majority of those births occurring between 32 and 37 weeks of pregnancy gestation (Howson et al., 2012). Approximately 15 million babies are *Born Too Soon*, as their document is titled, and more than a million infants die due to complications of prematurity (Howson et al., 2012). The majority of PTBs occur in 10 countries from sub-Saharan Africa, South Asia, and the United States. European countries have the lowest rates of PTBs. The outcomes for premature infants born in low-income countries are not as favorable as for those born in high-income countries. Many preterm infant survivors are left with hearing, vision, or intellectual problems that last a lifetime (Howson et al., 2012).

The definition of PTB distinguishes level of prematurity by weeks of gestational age. In the *Born Too Soon* (Howson et al., 2012) document, the subcategories are defined as moderate to late preterm being 32 to 37 weeks, very preterm as 28 to 32 weeks, and extremely preterm as less than 28 weeks' gestation at birth. Survival rates of infants born at less than 28 weeks are very low. The determination of gestational age to classify a neonate in any subcategory in developed countries is made by a combination of early ultrasound and mother's menstrual history (Howson et al., 2012). When ultrasound is not available or only ultrasound but not menstrual history is used, the determination of gestational age may not be as accurate and result in statistical differences when studying outcomes of PTB. In clinical practice, assigning an infant to the wrong subcategory of prematurity may result following a different standard of care. The New Ballard neonatal assessment tool was introduced in 1991 to include a more accurate gestational age physical assessment of the very preterm newborn and can be used in low-resource settings (Thompson, Levi, Bly, Ha, & Keirns, 2014). In addition to the New Ballard, practitioners have also used the Dubowitz score to assign a gestational age based on neurological and physiological examination (Dubowitz, Dubowitz, & Goldberg, 1970). Variations in results can occur but both methods can be easily taught to healthcare providers and require little in the way of resources (Anne Lee et al., 2017). Therefore, both assessments can be used in low-income, low-resource settings.

There is no one singular cause of preterm labor. For some women, preterm labor is the result of a combination of physical, psychological, and environmental factors (Yamamoto & Premji, 2017). Genetic factors can play a part in preterm labor (Smid et al., 2017) as well as prior history of spontaneous early labor (Hughes et al., 2017). Prior elective or spontaneous abortions have been identified as a risk factor for preterm labor in subsequent pregnancies (McCaffrey, 2017). Premature birth may also result from early induction of labor due to maternal conditions that are detrimental to mother or fetus or both. Many probable causes of preterm labor have been identified, although the occurrence of preterm labor is not always predictable. There are occasions when the interplay of multiple factors may result in preterm labor. A screening tool measuring the possible risk factors a woman may have would be ideal. An evaluation using such a tool could include items such as fetal fibronectin testing, observation of shortened cervical length by ultrasound, prior pregnancy history, presence of infection or inflammatory conditions, and known environmental exposures, all of which may be helpful in identifying women at risk for premature labor. Unfortunately, such a perfect screening tool does not exist. Historically, some women with several risk factors may not deliver prematurely.

Screening tools, ultrasounds, and other testing can only be effective if women make use of available prenatal care. Lack of insurance, lack of transportation, and lack of knowledge are some of the reasons women do not obtain prenatal care (Swartz, Hainmueller, Lawrence, & Rodriquez, 2017). In some countries and cultures, the need for early prenatal care and multiple visits are not viewed as necessary. The inability to form a meaningful relationship with a healthcare provider while garnering social and psychological support from friends and family may result in non-utilization of healthcare systems viewed as unreceptive to meeting the pregnant woman's needs (Nypaver & Shambley-Ebron, 2016). If a woman has had a pregnancy delivered at term without difficulties, she may decide that frequent visits with a care provider are necessary during a subsequent pregnancy, even if that pregnancy occurs within only months of the previous delivery. Lack of availability of appropriate healthcare facilities or trained care providers can also contribute to rates of PTBs, infant mortality, and increased need for preterm infant care (Susuman, Chialepeh, Bado, & Lailulo, 2016).

Preterm infants require specialized care to survive. There is great variation in the methods and effectiveness of care delivered to preterm infants between high- and low-income countries. Disparities in care available and delivered can also be found within geographic areas of the same country. Neonatal intensive care units (NICUs) have been found to be both underutilized and overutilized resulting in higher healthcare costs (Harrison, Wasserman, & Goodman, 2018). The cost of providing neonatal intensive care for vulnerable preterm infants adds a huge financial burden to the healthcare system. As gestational age decreases, the overall costs of care increase. Care costs more for extremely preterm infants who require more diagnostic or medical procedures, medications, longer hospital stays, and long-term care (Stephens, Lain, Roberts, Bowen, & Nassar, 2016). The Institute of Medicine (Berhman & Butler, 2007) estimates that the care of infants born at less than 28 weeks' gestation costs as much as 20 times that of infants born at 32 to 37 weeks' gestation. Preterm infants are also more at risk for hospital readmission within 6 weeks of birth, adding more to the financial burden (Soilly, Lejeune, Quantin, Bejean, & Gouyon, 2014). There are additional societal costs of prematurity which are seldom contemplated, such as early intervention services,

special education, and disability services for infants who survive with residual problems and loss of productivity by parents and caregivers (Berhman & Butler, 2007). The reality is that not all countries have the infrastructure or finances to aggressively treat all preterm infants. Some cultures are more accepting of infant death than others and do not expect all infants to survive regardless of the cost. However, there are some initial interventions that can be performed in any setting which can increase the chances of survival for many premature infants, even in low-resource nations.

Birth Weight

Birth weight is one of the most important determinants of the infant's future health (Howson et al., 2012). LBW is defined as an initial birth weight of less than 2,500 g and is further categorized as either very low birth weight (VLBW) or extremely low birth weight (ELBW). VLBW is defined as an initial birth weight of less than 1,500 g, and ELBW is defined as a birth weight of less than 1,000 g. Ideally birth weight should be measured within the first hour of birth before significant postnatal losses occur. In some cases, when the infant is in distress, the birth weight might be estimated until an accurate weight can be determined. The incidence of LBW in the United States was reported at 8.17% in 2016 (Martin et al., 2018). LBW infants are at higher risk for neonatal and postnatal morbidity and mortality. Being born LBW has implications for health as an adult and has been linked to cardiac and metabolic disorders later in adult life (Morrison et al., 2016). While survival for ELBW infants has improved with advances in neonatal care, the risk for neurodevelopmental impairment has increased (Schieve et al., 2016). As many as 50% of children born extremely preterm or at ELBW have residual effects of prematurity with cognitive, academic, or psychological problems when they are of school age and beyond (Schieve et al., 2016).

The macrosomic or large for gestational age (LGA) fetus also has risks. Pregnancy risk factors for being LGA include maternal obesity, maternal age older than 35, maternal diabetes, prolonged pregnancy longer than 41 weeks, abnormally tall or short maternal stature, and male fetus. LGA is defined as greater than 90th percentile for weight adjusted for gender and gestational weeks at delivery. Potential complications for the mother include prolonged labor with increased risk for cephalopelvic disproportion (CPD) and need for cesarean section. During vaginal delivery, the LGA infant is at great risk for injury such as stillbirth, brachial plexus injury as the result of shoulder dystocia, fracture of the clavicle, the need for ventilatory support, and mortality (Chauhan et al., 2017). In the period immediately following delivery, the macrosomic infant is at risk for hypoglycemia, polycythemia, and hyperbilirubinemia. Successful resolution of these conditions, if they occur, does not appear to have long-term effects on infant development (Khambalia, Algert, Bowen, Collie, & Roberts, 2017).

Determination of gestational age can be estimated prior to delivery or upon examination of the newborn. Additional physical measurements are obtained to determine if the infant weight and size are appropriate for the gestational age obtained. Gestational age can be based upon maternal history in combination with ultrasound when available, or physical assessment. After birth, the neonate's weight, frontal occipital head circumference, and length at birth are plotted on a graph to evaluate appropriateness of growth based on gestational age. The infant is categorized as appropriate for gestational age (AGA) if birth weight falls between the 10th and 90th percentile for his or her gestational age; small for gestational age (SGA) if birth weight falls into the lower 10th percentile for weight based upon gestational age; or LGA if birth weight is greater than 90th percentile for weight based upon gestational age, or more than 4,000 g. at any gestational age (Barth & American College of Obstetricians and Gynecologists, 2016). Identification of infants who are SGA or LGA helps assure they receive proper monitoring of blood glucose and early feedings if indicated.

Before birth, an estimated fetal weight (EFW) can be determined via ultrasound. Many fetuses who are classified as SGA (i.e., EFW below 10% for growth) might, in reality, be healthy and genetically small (Kiserud et al., 2018). Additional fetuses may be intrinsically small secondary to a chromosomal or environmental condition such as trisomy 18, fetal alcohol syndrome (FAS), or infection, such as cytomegalovirus. The remaining fetuses may have increased perinatal risk and have fetal growth restriction (FGR; Gordijn, Beune, & Ganzevoort, 2018)

FGR can be caused by maternal, fetal, or placental problems. Maternal causes include conditions such as preeclampsia; smoking or taking certain drugs can result in progressive uteroplacental insufficiency and limit the normal delivery of oxygen and nutrients to the fetus. Inadequate maternal nutrition, low prepregnancy weight, low weight gain in pregnancy, or inadequate prenatal care are other maternal causes of FGR. In developed countries where bariatric surgery is available, malabsorptive surgery has been associated with FGR (Chevrot et al., 2016). Fetal conditions that can contribute to FGR include fetal genetic factors, congenital infection, intrauterine crowding from multiple pregnancy, Rh isoimmunization, or twin-to-twin transfusion. Abnormal placental pathophysiology resulting in poor perfusion through the placenta, abnormal cord insertion, placental infarcts, or implantation issues such as placenta previa or abruptio placenta are also causes of FGR (Burton & Jauniaux, 2018; Kingdon, Audette, Hobson, Windrim, & Morgen, 2018). Severe uteroplacental insufficiency restricts blood flow to the fetus and affects fetal growth and oxygenation. To spare function of vital organs, the fetus enters a brain-sparing mode which accounts for changes in fetal growth. Oxygen and nutrients are prioritized to the brain, heart, adrenals, and placenta with vasoconstriction resulting in less circulation of oxygen to the kidneys, lungs, muscles, bone marrow, and gastrointestinal tract (Figueras et al., 2018).

Fetuses with FGR must be identified and closely monitored with nonstress testing, biophysical profiles, amniotic fluid volume estimates, contraction stress tests, and Doppler studies of maternal and umbilical vessels when available. Infants may be subject to preterm delivery and FGR due to altered placental implantation and function (Silver, 2015). **Emergency Alert: Preterm delivery is indicated if signs of fetal stress or distress are present.** After birth, infants with FGR often have problems with low blood glucose or thermoregulation due to a lack of subcutaneous fat. They also are at increased risk for necrotizing enterocolitis, thrombocytopenia, and renal failure because during fetal development, blood is shunted away from the gastrointestinal and renal system to the brain, heart, and other vital organs as a protective mechanism. Preterm delivery and FGR infants are at greater risk for necrotizing enterocolitis, retinopathy of prematurity, and increased incidence of neonatal jaundice (Platt, 2014). Prematurity and LBW when occurring together have also been identified as having an impact on neurodevelopment resulting in developmental disabilities and cognitive impairments (Howe, Sheu, Hsu, Wang, & Wang, 2016; Schieve et al., 2016). **Emergency Alert: Infants with low birth weight have also been found to be more at risk to develop a metabolic syndrome with insulin resistance, hypertension, hypercholesterolemia, and heart disease** (Mzayek et al., 2016; Pocobelli, Dublin, Enquobahrie, & Mueller, 2016).

Infant Mortality Rate

Neonatal deaths during the first 28 days of life accounted for 46% of deaths of children under age 5 in 2016, representing an increase from

41% in 2000 (United Nations Children's Fund [UNICEF], 2017). International disparities exist with some countries below or meeting the SDG for 2030 whereas others are still well above the goal. PTB complications are responsible for the majority of neonatal deaths worldwide (UNICEF, 2017). The world infant mortality rate (IMR) is estimated at an average of 19 deaths per 1,000 live births (UNICEF, 2017). Infants from low- or middle-income countries represent a higher percentage of neonatal deaths than infants from industrialized nations. PTB complications and intrapartum events represent the causes of 59% of neonatal deaths (UNICEF, 2017). Reducing neonatal deaths across all nations will have a major impact on progress toward achieving the United Nations SDG 3, which aims to "Ensure healthy lives and promote well-being for all at all ages" (UN, 2015). Because of a high percentage of PTBs, the United States ranked sixth internationally in the top 10 countries accounting for 60% of PTBs, lagging behind many European countries (Howson et al., 2012). PTBs and the resulting complications contribute to higher neonatal mortality. Neonatal mortality rates have declined in the United States but remain higher than comparable countries (Gonzales & Sawyer, 2017). Differences in interpretation of what constitutes fetal viability can account for some differences in how neonatal deaths are reported. Neonatal mortality in the United States was reported to be 3.93%, whereas infant mortality, that which occurs between 28 days and 1 year, was reported at 1.97% in 2015 (Murphy Xu, Kochanek, Curtin, & Arias, 2017). The majority of those deaths are attributed to prematurity followed by underlying perinatal causes responsible for birth defects, sepsis, cord or placental complications, maternal complications, and respiratory distress (MOD, 2016).

IMRs differ in the United States by race, ethnicity, and geographic region. The highest IMR was reported in infants born to non-Hispanic Black (NHB) mothers (11.73 deaths per 1,000 live births) compared with infants born to non-Hispanic White (NHW) mothers (4.82 per 1,000 live births; Murphy et al., 2017). Based on 2016 birth data in the United States, NHB mothers had a higher rate of delivering infants of LBW (<2,500 g) compared with infants of NHW mothers (Martin et al., 2018). Ethnic disparities are also evidently related to neonatal mortality during the first 28 days of life. Comparison rates for NHB and NHW infants for the three leading causes of neonatal death show that infants demonstrate disparities exist. Infants of NHB mothers had the highest rate of neonatal deaths related to congenital malformations, prematurity or LBW, and being affected by maternal complications of pregnancy compared with infants of NHW mothers (Murphy et al., 2017).

The birth complications of congenital malformations, prematurity, and LBW place newborns in danger of not surviving birth. Those infants who do survive frequently require care which may not be available in lower income countries, resulting in eventual mortality. Infants who are born in countries where neonatal care is more advanced may survive but will face a lifetime of future treatments and care for complications resulting from the original condition at birth.

Epidemiologic Paradox

Birth outcomes, such as risk for preterm labor, cannot always be predicted by the presence of maternal risk or sociodemographic factors (Yamamoto & Premji, 2017). For example, Mexican women who immigrate to the United States have demographic and socioeconomic factors such as high rates of teen pregnancy, less education, and higher rates of no prenatal care or late prenatal care in the third trimester that put them at high risk for poor perinatal outcomes. However, Asian Indian women who immigrate to the United States have demographic and socioeconomic risk factors similar to White women that put them at low risk. Asian Indian women have higher education levels with more college graduates, less teenaged pregnancy, and are more likely to initiate prenatal care in the first trimester. However, an "epidemiologic paradox" occurs, and outcomes do not occur as predicted. Black women have the highest incidence of LBW, SGA, and fetal and neonatal deaths in the United States (Purisch & Gyamfi-Bannerman, 2017). Foreign-born Mexican women with demographic and socioeconomic risk factors comparable to Black women have better than expected perinatal outcomes, including less LBW and less neonatal deaths (Murphy et al., 2017). In comparison, Asian women in the United States initiate prenatal care later, have lower incidences of preterm delivery, and have higher incidences of LBW and VLBW than White women (Murphy et al., 2017). This "epidemiologic paradox" suggests that there might be other factors that give foreign-born women either a perinatal advantage or disadvantage such as environmental factors, diet or lifestyle factors, or genetic factors (Mehta-Lee, Palma, Bernstein, Lounsbury, & Schlecht, 2017; Rood & Buhimschi, 2017).

MATERNAL RISK FACTORS

Evaluation of maternal risk factors can help anticipate many of the neonates who will be at increased risk for problems at birth. There is no way to accurately predict every neonate who will be at risk since a cause-and-effect relationship between high-risk maternal characteristics or behaviors and poor outcomes is not always clearly defined. For example, there have been cases of identical twins where one twin was born healthy and the other one required admission to the NICU. Although both babies had similar genetic makeup, gestational age, and exposure to the same in utero environment, only one of them had problems.

One of the most essential ways to decrease problems of prematurity, LBW, and perinatal death is to promote optimal pregnancy health. The ideal state is for all women considering pregnancy to seek preconceptual counseling. During the preconceptual visit, the woman can learn about risk factors that could potentially cause birth defects or problems with pregnancy. Risk factors may be either modifiable or nonmodifiable. Examples of modifiable risk factors that can be changed include diet, smoking, alcohol use, and substance use or abuse. Nonmodifiable risk factors are intrinsic factors that can't be changed such as maternal age, ethnicity, genetic inheritance, or preexisting health problems. Risk factors usually do not occur in isolation. The presence of one risk factor may lead to other risk factors, causing an additive effect. For example, a pregnant woman who lacks financial resources might also have a poor obstetric history, an inadequate nutritional intake, increased stress, and nicotine addiction. Some maternal risk factors can be modified through patient education, counseling, lifestyle changes, and support. The purpose of preconceptual care is to help the woman who is contemplating pregnancy get into optimal physical condition for childbearing prior to conception. Unfortunately, preconceptual counseling is not the norm. Therefore, all women of childbearing age must be encouraged to live healthy lifestyles and to seek early prenatal care in the first trimester of pregnancy. Even the first trimester of pregnancy is not too late to implement interventions or modify lifestyle risk factors that will maximize positive pregnancy outcomes.

Maternal risk factors consist of demographic, behavioral, and psychosocial factors, as well as maternal medical conditions and pregnancy-related conditions. Demographic risk factors include ethnicity, age, socioeconomic status, occupation, and environmental or work-related exposures. Psychosocial risk factors include

social, behavioral, stress-related, or maternal psychological conditions. Medical risk factors for prematurity that are unalterable can vary by population and can include previous obstetric events (i.e., previous history of infertility or pregnancy loss) or pregnancy-related conditions that only happen during pregnancy such as multiple gestation, pregnancy-induced hypertension (PIH), or gestational diabetes. Modifiable risk factors include low prepregnancy weight, low or high body mass index (BMI), and behavioral risk factors the mother has either prior to or during pregnancy. Examples of behavioral risk factors that can possibly be harmful to the fetus include inadequate dietary intake, smoking, or substance abuse (drugs or alcohol).

A complete maternal history done at the first prenatal visit will help identify important demographic and medical risk factors that might influence the outcomes of the pregnancy. A variety of demographic factors are related to neonatal outcomes. The presence of risk factors should serve as a warning. Many women with identifiable high-risk factors will give birth to healthy infants without problems. The potential influence of demographic risk factors of age, ethnicity, obstetric history, and the health-compromising behaviors (HCBs) of nutrition, smoking, alcohol, and drug use upon pregnancy will be further discussed.

Maternal Age

Maternal age is considered to be a risk factor for poor perinatal outcomes at either end of the childbearing age spectrum. The maternal childbearing age range has widened over the past decade partially due to advances in assisted reproductive technology (ART) that have made it possible for women to achieve pregnancy, even into the fifth or sixth decade of life, if desired. Worldwide, the maternal age at the time of the birth of the first child ranges from a mean of 18.1 in less developed populations to a mean of 28.5 years in more industrialized nations (Central Intelligence Agency, n.d.).

There is conflicting evidence that adolescent pregnancy increases the risk of adverse outcomes. Some adverse outcomes could be due to societal socioeconomic conditions. Younger adolescent mothers (15.9 years of age or younger) have demonstrated increased risk for complications of anemia, preterm delivery, postpartum hemorrhage, and preeclampsia. Older adolescents (16–19.9 years of age) have presented a higher risk for needing blood transfusions in addition to increased risk for anemia and preterm delivery (Kawakita et al., 2016). Adolescent mothers younger than age 20 are considered to be especially high risk because they are biologically immature and have not had the chance to complete their own physical growth and reproductive development (Brosens et al., 2017). Reproductive immaturity can increase risks of a fetal loss, PTB, or infant death.

In 2016, the U.S. teen birth rates for ages 15 to 19 years declined dramatically to a rate of 20.3 births per 1,000 births, representing a decline of 9% since 2015 (Martin et al., 2018). Even so, the United States has one of the highest teen birth rates worldwide compared with other developed nations. Numbers of teen and adolescent births globally are difficult to estimate, but rates are higher in countries where child marriage is allowed. Child marriage rates are declining in many countries due to the efforts of numerous stakeholders—for example, The Programme introduced by the United Nations Population Fund (UNFPA) and UNICEF (UNFPA-UNICEF, 2017). The Programme is intended to increase educational levels of the female population and teach necessary life skills and decision-making principles. In countries where there has been success, the age of first birth has increased and girls completing the Programme are planning fewer children and a limited number are using birth control (UNFPA-UNICEF, 2017). In the United States, the rate of unmarried teen births has dropped to 18.5 births per 1,000 deliveries (Martin et al., 2018). However, there are many countries where unmarried teen pregnancy rates are high. Teen mothers and their infants have increased perinatal risks including higher risk of dying during childbirth compared with 20-year-old women. Infants of teen mothers have an increased risk of dying within the first year of life (WHO, 2018a). There are also lifelong disadvantages for younger teen mothers who have less years of formal education. Education is known to be a factor related to promotion of positive pregnancy behaviors. Pregnant adolescents who are less educated most likely will not use contraception, may not recognize danger signs in pregnancy that something is wrong, or may not even seek prenatal care. In the United States, many programs directed at preventing teen pregnancy focus on education in general and are specifically related to attitudes, prevention, and community support (Bhuiya et al., 2017; Galloway, Duffy, Dixon, & Fuller, 2017). Unmarried teen mothers require financial support for the pregnancy from parents or social agencies. Many teen mothers find it difficult to remain in school while pregnant or return to school full-time following delivery. The parenting role is difficult without financial support or help with day care from their parents (Kumar, Raher, Ware, & Phipps, 2017). Dropping out of school during pregnancy can make it difficult to return and complete their education, limiting employment opportunities in the future. Some teen girls drop out of school or leave home due to poor family relationships even before getting pregnant. Globally, the acceptance of adolescent pregnancy by families and communities differs sometimes, resulting in fear of stigmatization, family shame, and additional stress (Aziato et al., 2016). Preexisting maternal disadvantages, not young maternal age, are more likely to account for negative outcomes of teen parenting for mothers and infants (McHugh, Kvernland, & Palusci, 2017). A need has been identified for improved parenting information for teens, as well as improved medical knowledge and continued healthcare access (Dumas, Terrell, & Gustafson, 2018). Teen mothers are also more likely to have a repeat teen pregnancy. In 2016, about 17% of teen births in the United States were the mother's second, third, or fourth child (U.S. Department of Health and Human Services, n.d.).

Advanced maternal age refers to women who are older than 35 at the estimated date of delivery. Women may have problems conceiving secondary to infertility, or some women may choose to delay childbearing voluntarily while pursuing educational or professional goals. A recent trend has been an increase in the number of women in the advanced maternal age group who are having babies. Advances in reproductive science, such as oocyte donation, have made it possible for women who are postmenopausal in their 50s or 60s to conceive. The birth rate for women ages 40 to 44 was 11.4 births per 1,000 women and the birth rate for women ages 45 to 49 increased in 2016 to 0.9 births per 1,000 women (Martin et al., 2018). Advanced maternal age poses increased risks for decreased fertility, chromosomal abnormalities in the infant, spontaneous abortion, and preterm delivery (Frederiksen et al., 2018; Waldenström, Cnattingius, Vixner, & Norman, 2017; Wesselink et al., 2017). Late fetal and early perinatal death rates are higher for pregnant women 40 and older than for any other age groups. Pregnant women older than 40 have a higher rate of spontaneous abortion than pregnant women between the ages of 20 and 24 (Frederiksen et al., 2018). Women older than 35 are at increased risk for perinatal mortality; however, the increased risk appears to be related to previous obstetric and medical comorbidities more than age (Morris, Totterdell, Bin, Ford, & Roberts, 2018). Although fertility tends to decline with advanced maternal age, women between the ages of 35 and 39 actually have an

increased risk of conceiving twins without the assistance of fertility treatments. Women over age 40 having twins are at less risk to have a preterm infant than 15- to 17-year olds at each gestational age (i.e., <32, <34, and <37 weeks; McLennon et al., 2017). Older women also are more likely to have multifetal pregnancies due to use of assistive reproductive technologies, which could account for increased maternal morbidity (Moaddab et al., 2017; Witteveen, Van Den Akkar, Zwart, Bloemenkamp, & Van Roosmalen, 2016). Current guidelines suggest practitioners screen for maternal genetic disorders and medical disorders and avoid multifetal implantation while attempting single gestation pregnancies (Sumners, Echer, & Hearns-Stokes, 2016).

Older pregnant women are at an increased risk for medical problems associated with aging such as cardiac disease and chronic hypertension (Morris et al., 2018). The rates of medical complications including diabetes, cardiac disease, and hypertension in pregnant women increase as maternal age advances. Diabetes increases their risk for delivery of a macrosomic infant. Pregnancy over 48 years of age can also contribute to increased risks of gestational hypertension, gestational diabetes, and placenta previa (Fitzpatrick, Tuffnell, Kurinczuk, & Knight, 2016). Fitzpatrick et al. (2016) also found that women of advanced maternal age usually planned the pregnancy, expected and participated in more prenatal visits, and took part in more prenatal assessment testing.

Advanced maternal age creates genetic risks because as the woman gets older, the genetic material contained within her ova ages. The prevailing theory is that all females are born with all of the oocytes they will ever have, which contain the genetic material that she will pass on to her progeny. According to maternal aging theory, as the woman ages, her oocytes and the genetic material contained within also age. Aging genetic material is more likely to have errors during cell division and migration during meiosis that can result in aneuploidy (an abnormal number of chromosomes), lower implantation rates, decreased fertility, or increased risk of spontaneous abortion (Moaddab et al., 2017; Wesselink et al., 2017). Chromosomal disorders increase with advanced maternal age. Although chromosomal disorders can occur at any maternal age, there is an increased risk after age 35. **Quality & Safety: Advances in screening tests now allow practitioners the advantage of offering testing appropriate to the low- or high-risk status of a patient** (Dashe, 2016).

PATERNAL FACTORS

Paternal age does not appear to be an independent factor in adverse pregnancy outcomes such as disparities in fetal growth or genetic disorders (Hurley & DeFranco, 2017). However, the use of ART increased as paternal age increased. The use of ART has been associated with nonchromosomal birth defects, LBW, and placental complications (Luke, 2017). Increases in childhood cancers have been observed with advanced ages of both mother and father, with increased risk for non-Hodgkin lymphoma influenced by paternal age only (Wang et al., 2017). Paternal socioeconomic position has been associated as a factor with LBW in infants of African American women when controlled for maternal factors (Collins, Rankin, & David, 2016). Advanced paternal age should also be considered when evaluating prenatal risks, as it has been associated with rare congenital anomalies in offspring due to dominant mutations such as neural tube defects (Prasoona et al., 2016). **Quality & Safety: A careful assessment of the family history of both parents will help alert the healthcare provider to potential risks.**

Paternal environmental or occupational exposure to certain chemicals can lead to developmental outcomes including altered growth, structural or functional abnormalities, or death. Some effects may be expressed across the lifetime of the child (Yen et al., 2016). High levels of paternal occupational exposure to lead have been linked to LBW (Craft-Blacksheare, 2017). Paternal exposure to occupational and environmental toxins may continue throughout the child's lifetime.

LIFE COURSE DETERMINANTS OF BIRTH OUTCOMES AND WEATHERING

The life course theory (LCT) is an approach that is being used to explain health, disease, and health disparities across populations and over time. Rather than focusing on ethnic or genetic differences or an individual's choices to explain health disparities, the LCT focuses on social, economic, and environmental factors as key determinants that help shape health or disease in communities and populations. The LCT acknowledges the importance of intergenerational preprogramming (i.e., maternal preconceptual health) and prenatal preprogramming (i.e., the in utero environment) in influencing fetal and child health. While health can be impacted at any time, there are critical and sensitive periods when events can have a maximal impact on lifetime health such as during fetal development, early childhood, or adolescence. The goal would be to promote interventions during these sensitive times to maximize health (UN, 2015).

Applying the LCT perspective to preterm delivery would propose that reproductive and birth outcomes are the product of circumstances and events that occur not only during pregnancy but throughout the life of the mother, beginning either before or at the time when she was conceived. The LCT perspective acknowledges the possibility that early-life experiences can shape health across an entire lifetime and could potentially influence the health of future generations (Yingwattanakul & Moschis, 2017). According to the LCT perspective, it is not enough to assess the woman's experiences during the immediate preconceptual and prenatal period to determine risks for poor outcomes. Assessment of major events during her entire life course and the effects of material deprivation, social disadvantage, discrimination, and marginalization must be explored (Nist, 2017). The health consequences of poverty and race-based discrimination and the health effects of chronic stress from having inadequate resources to meet demands must also be considered. For example, exposure to poor nutrition as a child, or even as a developing fetus, could impact a woman's pregnancy outcomes. The life course perspective aligns with the developmental origins of health and disease approach, which posits the important role of the fetal in utero environment in development of structure and functions of organs of the body. For example, a lack of folic acid during development can lead to neural tube defects; exposure to tobacco can lead to LBW or short gestation; and exposure to maternal antidepressants may cause PTB and increased risk of neonatal morbidity (Eke, Saccone, & Berghella, 2016; Nörby et al., 2016; Trinidad & Wick, 2017). Components of a perinatal life course risk assessment tool are not yet developed; however, this area of study offers intriguing promise to unravel some possible explanations for healthcare disparities.

PSYCHOLOGICAL STRESS IN PREGNANCY

Maternal mental health and psychological stress are increasingly being studied as possible sources of adverse perinatal outcomes. Stress is an interaction between the person and environment in which there is a perceived discrepancy between the demands of the environment and the individual's resources (i.e., psychological,

social, or biological) for dealing with it. During pregnancy, women may experience many types of stressors. Chronic life stressors include stress about finances, work situations, difficult relationships, health concerns of self or other family members, or other factors. Acute stressors during pregnancy include situational crisis or natural disasters. There is a growing body of evidence related to the effects of acute and chronic maternal stress during pregnancy on gestational length and birth weight (Nkansah-Amankra, 2018). Other evidence points to associations between preconceptual stress and accumulated life stress on birth outcomes.

Acute and chronic stressors can occur due to life events such as the death or serious illness of a loved one, previous traumatic event, or any social or economic stressors. Rosenberg, Li, and Seng (2017) suggested the use of the concept of allostatic load in nursing research. Stress in either the acute or chronic form affects pregnancy outcomes. When the body experiences stress, there is a physiological reaction. Chronic stress results in physiological dysfunction over time that impairs the immune response and produces metabolic and cardiovascular changes that produce illness. Increased stress during pregnancy can result in normal stress reactions causing increased physiological response, which is harmful to the pregnancy. A woman may be entering her pregnancy unknowingly in a poor physiological state at risk for hypertension and diabetes due to these changes. Maternal exposure to severe life events, such as death or serious illness in close relatives, witnessing or experiencing physical violence as a child or adult, or having experienced an adverse birth outcome previously, can place the woman at risk for adverse pregnancy outcomes (Margerison-Zilko, Strutz, & Holzman, 2017; Shaw et al., 2017). Labor and delivery may trigger a response in women who suffer from posttraumatic stress disorder (PTSD) resulting from prior adverse pregnancy outcome or sexual assault. Healthcare providers should evaluate all patients who exhibit signs of depression in pregnancy to rule out PTSD so the patient receives the proper psychologic support (Geller & Stasko, 2017). PTSD has been identified in women who have had a diversity of acute traumatic events in their life. The diagnosis and effect on pregnancy outcomes can be found in all countries, ethnic groups, and socioeconomic levels. Intimate partner violence has been identified as a chronic stressor and as a cause of PTSD in women, which can have a negative impact on pregnancy and result in LBW and preterm delivery (Karakurt, Patel, Whiting, & Koyutürk, 2017).

Pregnancy-related anxiety is a form of anxiety specific to pregnant women and includes worries about the health and well-being of the baby, impending labor and birth, hospital and healthcare experiences and one's own health and survival, and about parenting and the maternal role. Pregnancy-specific stress includes: (a) fear of pain; (b) pregnancy-related concerns about the health of the baby, labor, and delivery or body size and body image; (c) pregnancy-specific support and giving birth; and (d) pregnancy-related symptoms and attitudes toward whether the current pregnancy was intended or wanted (Westerneng et al., 2017). Pregnancy-specific anxiety can result in detrimental health behaviors such as smoking and dieting to avoid excessive weight gain (Westerneng et al., 2017).

Major stressors such as life events, major catastrophes, chronic strain, neighborhood stress, and multiple stressors may contribute to PTB, gestational age, or gestational length. The exact mechanism by which maternal stress causes preterm labor is not fully understood, but it is thought to occur by one of two mechanisms. Corticotropin-releasing hormone released as a by-product of maternal stress could stimulate neuroendocrine pathways within the maternal–fetal–placental unit that trigger labor; or maternal stress could cause increased maternal and fetal susceptibility to inflammation and infection, triggering labor through an immune-inflammatory pathway (Rosenberg et al., 2017; Sultana et al., 2017). These interactions between neuroendocrine, immune, and behavioral processes may be tempered by maternal resilience resources (ego strength, personality, social, coping, cultural values, and worldview). Hardiness, resilience, and social support might act as stress buffers in some women, lessening the impact of stress (Scoglio et al., 2018).

Not all women are affected in the same way by stress, which could account for difficulty with prediction of outcomes. Critical periods may occur during pregnancy where there is altered vulnerability to the effects of prenatal stress. The cumulative effects of lifetime exposure to acute stress and experiences of chronic day-to-day stress increase the risk of stress-related disease during pregnancy and may help explain some ethnic disparities in birth outcomes (Margerison-Zilko et al., 2017). Just as it is difficult to predict the outcomes related to stress, it is imperative to assess for the methods pregnant women may use to cope with stress prenatally.

Smoking has been cited by many as a method to deal with stress. Tobacco use often rises in periods of increased stress. Many women attempt to reduce or quit smoking prior to conception or during pregnancy once they are made aware of the dangers of perinatal complications (Damron, 2017). Exposure to second-hand smoke also carries the risk of lower birth weight and PTB in addition to making it difficult for the mother to quit herself. Unfortunately, women of lower socioeconomic status are more likely to persist with smoking in pregnancy and also have higher rates of comorbidities of hypertension and diabetes (Martin et al., 2018). Alcohol use has also been identified as a stress reduction strategy by some individuals. The use of alcohol in pregnancy can have the outcome of SGA and postnatal growth restriction (Carter et al., 2016). As there is no accurate method of determining how much alcohol is too much nor if the timing of drinking changes the outcome of FAS disorder, it is best to advise no use of alcohol during pregnancy (Wilhoit, Scott, & Simecka, 2017). Alternative stress reduction measures can be advised by care providers to improve pregnancy outcomes.

Physical activity such as walking can reduce the incidence of gestational hypertension and diabetes (Garland, 2017). Care providers may need to dispel the common myths about activity increasing the risk of miscarriage and make an individual assessment of the suitability of the activity for patients. In identifying a safe area for the patient to walk prenatally, the provider has also informed the patient of a possible safe area to bring the infant. Yoga is another intervention that some women may already practice and has been found to be useful in the treatment of anxiety and depression in the general population (Butterfield, Schultz, Rasmussen, & Proeve, 2017). Many of the moves and poses can be adapted for pregnancy. In addition to alternatives, providers can offer smoking cessation programs and support to mothers as quitting at any time during pregnancy will improve neonatal outcomes (Wallace, Aland, Blatt, Moore, & DeFranco, 2017). The success of any intervention will depend on the appropriateness for the individual client.

OBSTETRIC FACTORS

Obstetric history is a good indicator of the presence of maternal risk factors. Women with previous obstetric complications are more at risk for problems with the current pregnancy. Previous obstetric history of infertility, stillbirth, preterm infant, infant with growth restriction or congenital anomalies/genetic problems, complications during pregnancy or birth, or other poor outcomes are

clues that indicate that the pregnancy must be closely monitored. Prepregnancy health status is another factor associated with the risk of preterm delivery. Women who are in poor physical condition prior to conception (i.e., underweight, having poor prepregnancy physical function, chronic hypertension, or smoking before pregnancy) have an increased risk for preterm delivery (Purisch & Gyamfi-Bannerman, 2017). Important obstetric factors that can compound pregnancy risk are the adequacy of prenatal care, the number of previous pregnancies, interpregnancy level, the use of ART, and postterm pregnancy (Frederiksen et al., 2018; Malacova et al., 2017; Howson et al., 2012).

PRENATAL CARE

Prenatal care that begins in the first trimester of pregnancy and continues until birth helps promote good birth outcomes. Most women seek prenatal care during the first trimester of pregnancy. Only about 6.2% of U.S. women start prenatal care during the last trimester or have no prenatal care, with higher rates of late or no prenatal care seen in NHB and Hispanic women compared with NHW women (Martin et al., 2018). WHO has set a worldwide goal for a minimum of eight focused antenatal care visits during pregnancy (WHO, 2016a). Worldwide, only half of women had four prenatal visits as previously recommended (UNICEF, 2018). Inadequate prenatal care increases the risk for LBW, PTB, and perinatal death (Hug, Sharrow, & You, 2017; Swartz et al., 2017). Increased death rates are seen in infants of women who did not have prenatal care, which might be associated with lack of access to care providers or lack of use of pediatric medical care resulting in untreated complications of pregnancy or neonatal infection (Murphy et al., 2017).

The decision to seek prenatal care is influenced by the woman's attitudes toward pregnancy, cultural preference, or lifestyle factors. For some women, access to prenatal care is limited due to financial constraints or geographic availability of a trained practitioner. Having six prenatal visits prior to delivery was considered a protective factor against LBW and prematurity. Current recommendations by WHO (2016a) encourage group antenatal care contact as well as private contacts as a means of encouraging pregnant women to engage in antenatal care, improve satisfaction, and decrease adverse pregnancy outcomes.

Providing care to the mother at delivery by a skilled birth attendant could also improve outcomes through early recognition of problems during labor and intervention. Worldwide, there are many countries where a majority of women deliver at home with or without the assistance of a trained practitioner. Countries with the highest rates of unattended births also have the highest rates of infant mortality (Hug et al., 2017). The United Nations SDG 3 (2015) seeks to provide universal access for all women to reproductive care including access to prenatal care and family planning information.

PARITY

Parity or number of previous deliveries has been considered another risk factor for preterm delivery, LBW infant, and abnormal placental implantation. Parity is difficult to disassociate from age as women with higher parity are usually older. Eugene and Abedinego (2017), in an age-matched case–control study, found adverse pregnancy outcomes appeared to be related to maternal age, education level, and socioeconomic status rather than grand multiparity. In general, primiparous women older than 35 years of age and multiparous teens younger than 18 years of age have an increased risk for PTB at any gestational length; however, there are some racial differences. Both primiparous and multiparous Black and Hispanic women have an increased risk for very PTB starting at a younger age (25 years). Primiparous teenagers tend to have the highest risk of having an extremely PTB (EPTB). The incidence of EPTB is higher in older primiparous Black and Hispanic women compared with teenagers. On the other hand, in White women EPTB risk is highest at either end of the age spectrum for both teenagers and older primiparas. However, for all races, the risks for any type of PTB increase as women are older than 40 years of age (MOD, 2016).

INTERPREGNANCY LEVEL

Interpregnancy level is defined as the amount of time between delivery of a baby and the subsequent conception of another child. Short interpregnancy level of less than 6 months increases the risk for maternal complications, including third-trimester bleeding, prelabor rupture of membranes (PROM), puerperal endometritis, anemia, and maternal death. Women with longer interpregnancy levels have the highest risk for preeclampsia, eclampsia, and gestational diabetes, again probably related to older maternal age. The risk for prematurity is increased when the interpregnancy level is less than 18 months and should be considered when providing postpartum care (Stuebe, Auguste, & Gulati, 2018). Programs developed to educate all women regarding family planning and appropriate birth intervals can help prevent the adverse outcomes of shortened interpregnancy level (Cross-Barnet et al., 2018).

ASSISTED REPRODUCTIVE TECHNOLOGY

ART is any procedure or medical treatment used to assist a woman to achieve pregnancy. ART is an option for many couples who have a history of infertility. ART methods include the use of medications to stimulate ovulation and release of eggs, or procedures where eggs and sperm are removed and mixed outside of the body to achieve fertilization. Some techniques require that the fertilized egg remain outside the body for a few days before being implanted back into the woman's body. In some cases, the eggs, sperm, or embryos might be frozen for later use or manipulated with instrumentation during the earliest stages of cell formation.

According to the CDC, about 1.7% of U.S. pregnancies are conceived using ART (CDC, n.d.-b). ART increases the risk for multiple pregnancy, prematurity, and LBW. Previously, many types of ART procedures resulted in high rates of multiple gestation pregnancies to describe triplet and greater gestation since couples may choose to have multiple embryos implanted to maximize their chances for success. More recent statistics in the United States demonstrate a higher rate of singletons and very few triplets (CDC, n.d.-a). The risk of prematurity increases with twins and higher order multiples. The identified risks involved with multiple gestation pregnancy prompted the American College of Obstetricians and Gynecologists (ACOG) to advise that providers limit the number of embryos transferred, use low-dose ovarian stimulation protocols, and educate clients regarding the risks inherent in higher order multiple gestation (Sumners et al., 2016). Multiple gestation pregnancy naturally increases risks for preterm labor (PTL), cesarean delivery, and LBW and provides one explanation for the increase in number of LBW and preterm infants over the past few years. However, the risk for prematurity and LBW exists for even singleton pregnancies conceived with ART (Luke, 2017). The Massachusetts Outcomes Study of Assisted Reproductive Technology provided data that demonstrates subfertile women with singleton pregnancies were at increased risk for developing gestational

hypertension, gestational diabetes, and delivering preterm (Luke, Gopal, Cabral, Stern, & Diop, 2017). The risk was present regardless of whether the client used ART to achieve pregnancy. Clients conceiving using in vitro fertilization (IVF) had the additional increased risk of fetal malpresentation, placenta previa, placental abruption, and delivery by cesarean section.

Couples who electively conceive through ART with a large number of embryos may have to make tough ethical decisions, including options for selective reduction later in the pregnancy, in order to protect the health of compromised fetuses. The risk for prematurity and LBW increases as the numbers of fetuses increase, increasing risks of poor outcomes for the infants. The decision to maintain a pregnancy with a large number of fetuses can be economically and emotionally catastrophic for the family. Outcomes for the babies who survive depend in part upon the number of fetuses and gestational age at delivery. Maternal care provider organizations have suggested limits on the numbers of embryos that can be implanted during ART procedures to help address some of these issues (Sumners et al., 2016). Continued research to improve ART techniques to assure success of singleton pregnancies will do much to impact outcomes of ART pregnancies.

POSTTERM PREGNANCY

Postterm pregnancy is defined as a pregnancy that continues past 42 weeks (294 days) or 14 days past the estimated due date (ACOG, n.d.). The cause of postterm pregnancy is not known, but it occurs more often with male fetuses and may have a genetic basis. Some cases of postterm pregnancy can be attributed to inaccurate dates used to calculate the estimated date of confinement. Ultrasound dating of pregnancy is considered to be accurate if done during the first trimester; however, ultrasound dating of pregnancy has a margin of error.

Postterm infants are more likely to have macrosomia, with increased risks for prolonged labor or CPD with increased risk for cesarean section, or shoulder dystocia with increased risks of possible musculoskeletal injury (i.e., fractured clavicle or brachial plexus injury). Postmaturity also predisposes to uteroplacental insufficiency, resulting in intrapartum asphyxia and meconium aspiration (N. Walker & Gan, 2017). These infants are more at risk for cord compression due to oligohydramnios and presence of meconium-stained amniotic fluid (Karahanoglu et al., 2016). Postterm pregnancy has also been related to lower umbilical artery pH levels and more frequent NICU admissions (Karahanoglu et al., 2016). The risk for cesarean section and associated complications also increases as pregnancy progresses beyond full-term (N. Walker & Gan, 2017). ACOG recommends close surveillance of postterm pregnancies between 41 and 42 weeks due to increased risks of complications as gestational age advances. Postterm fetuses should be evaluated by nonstress testing or biophysical profiles. Cervical ripening and induction of labor at 41 weeks is an alternative approach for management of postterm pregnancies when combined with appropriate fetal assessments (Dekker, 2016).

UNFAVORABLE HEALTHCARE BEHAVIORS

Personal habits such as smoking, illicit drug use, or alcohol use can compromise overall maternal health during pregnancy and can negatively influence fetal well-being. Prepregnancy maternal health status and poor health behaviors can play a role in PTL risk. Babies born to mothers who smoke, drink alcohol, or take drugs weigh less than babies of mothers who do not smoke, drink, or take drugs (Martin et al., 2018). Inadequate nutrition, over-the-counter or prescribed drug consumption, and environmental factors may create other HCBs and increase risks during pregnancy.

Smoking

Smoking is a major predictor of LBW, possibly due to impaired oxygen delivery (hypoxia) and nutrient delivery from the mother to fetus (Slemming, Bello, Saloojee, & Richter, 2016). Infants of mothers who smoke have an increased risk of premature rupture of membranes, intolerance of labor, and NICU admission (Wallace et al., 2017). Risk of adverse outcomes decreases with smoking cessation. Recent popularity of nicotine delivery systems such as e-cigarettes results in delivering the same neurotoxic effects as tobacco smoking. Unfortunately, some pregnant women have the perception that using e-cigarettes is less harmful than regular cigarettes and can be used to help in smoking cessation (Bhandari et al., 2018). Women who smoke are more likely to use alcohol or illicit drugs during pregnancy than those who do not smoke. In an analysis of national data, Kurti et al. (2017) identified a correlation with cigarette smoking, e-cigarette use, and use of illicit drugs. The effect of smoking on pregnancy outcomes is also dose dependent with heavy smokers more likely to have infants who are born extremely preterm (Dahlin, Gunnerbeck, Wikström, Cnattingius, & Edstedt Bonamy, 2016). Smoking rate in the United States during pregnancy has been estimated to be 7.2% with ethnic variations. More NHW women (10.5%) smoke during pregnancy as compared with NHB women (6.0%) and Hispanic women (1.8%; Martin et al., 2018).

Substance Use or Abuse

Substance use and abuse is a concern for childbearing women of all ages. Marijuana smoking has been associated with increased neonatal neurological morbidity and neonatal infection morbidity independent of confounding factors (Metz et al., 2017). Subjects of this study (Metz et al., 2017) also reported cigarette smoking and illicit drug use. Women under the influence of mind-altering substances are more likely to make poor choices and have an increased risk of engaging in unprotected sex resulting in an unplanned pregnancy. Additional studies have identified marijuana when used alone or combined with cigarette smoking to be significant in increased risk of PTB and LBW (Chabarria et al., 2016; Leemaqz et al., 2016). The effect of marijuana on pregnancy outcomes will become more apparent as more states legalize medicinal and recreational use.

Maternal alcohol ingestion during pregnancy can result in fetal alcohol spectrum disorders (FASD). The incidence of FASD may be related to both environmental exposure and genetic susceptibility. Alcohol is believed to have a direct teratogenic effect that limits fetal growth and brain growth. The fetal effects of drinking are most pronounced if the fetus is exposed during the first trimester of pregnancy. The minimum amount of alcohol that is harmful to the fetal brain is not known. It is known that binge drinking (ingestion of more than five drinks at one occasion) leads to higher levels of blood alcohol. Binge drinking is a special concern in early pregnancy when the fetal brain is developing and women may not yet realize that they are even pregnant (D. S. Walker, Edwards, & Herrington, 2016). In addition to being SGA, the neonate exposed to alcohol prenatally may have problems with sucking, which results in feeding problems (Wilhoit et al., 2017). Neonates who have been exposed to alcohol at any time prenatally can develop symptoms of FASD. Neonates who are SGA at birth may have continued postnatal growth restriction (Carter et al., 2016). Healthcare providers need to accurately assess women prenatally for alcohol use to be more prepared for possible adverse outcomes.

Research has identified the combined use of alcohol, smoking, and illicit drug use in multiple populations of pregnant women (Cohen, Osorio, & Page, 2017; Myers et al., 2018).

Illicit drug use in pregnant women is inclusive of misuse or abuse of prescription drugs and use of illegal substances. Illegal drug use crosses all socioeconomic sectors with the prevailing drug of choice initially being what is available and affordable. The use of crack cocaine has been more prevalent among more marginalized populations. Neonates of mothers who use crack cocaine are at higher risk of FGR and placental abruption (Butler, Rehm, & Fisher, 2017). As noted by Cohen et al. (2017), most drug use occurs in combination with other harmful substances. Pregnant women using illicit drugs also tend to enter prenatal care later in their pregnancy. Research that focuses on smoking, alcohol, and illicit drug use often relies on self-report by subjects, which may lead to some inaccuracy in findings (Morean et al., 2018). However, it is clear that the result of polypharmacy habits of the mother can result in PTB, LBW, and possible neonatal abstinence syndrome in the neonate (Kozhimannil, Graves, Levy, & Patrick, 2017; Zhao, McCauley, & Sheeran, 2017). Opioid use, both prescribed and illicit, has increased in the United States and resulted in multiple methods of treatment for mother and infant. There are challenges to treating the mother for addiction during pregnancy without having detrimental effects on the neonate (McCarthy, Leamon, Finnegan, & Fassbender, 2017). Treatment options for the neonate presenting with neonatal abstinence syndrome also vary based on the severity of symptoms and provider preference (Kraft, Stover, & Davis, 2016). See Chapter 30, Neonatal Abstinence Syndrome, for more information.

Nutrition

Adequate nutrition prior to conception and during pregnancy is important for maternal and fetal health. The pregnant woman needs to consume enough calories and nutrients to meet her own physiological needs as well as those of the developing fetus. Nutritional risks to consider include inadequate or excessive weight gain, medical conditions that complicate pregnancy such as hyperemesis gravidarum, dental conditions that compromise the ability to take in food, or inadequate resources to access food. Lack of adequate nutrients prior to or during early pregnancy can lead to birth defects. The importance for all women of childbearing age (between 15 and 45) to consume at least 400 mcg of folic acid daily to help prevent neural tube defects has been well established. The World Health Organization continues to recommend supplemental folic acid daily beginning prenatally if possible (WHO, 2016a).

Another important nutritional consideration is prevention of maternal anemia during pregnancy. Anemia is a serious problem affecting about half of pregnant women worldwide. It is more prevalent in nonindustrialized nations due to poor nutrition, iron-deficient diets, presence of parasitic disease, and incidence of HIV/AIDS. Women who are anemic are less likely to withstand blood loss during delivery and have increased risks of perinatal death, LBW, stillbirths, and prematurity. Promoting adequate nutrition prior to pregnancy is a key to improving outcomes of pregnancy. WHO (2016a) recommendations in nonindustrialized nations encourage the intervention of 120 mg of elemental iron and 2.8 mg of folic acid weekly to prevent anemia if daily dosing is not acceptable. Unfortunately, not all women take the recommended supplements due to a cultural belief that anemia is normal and expected in pregnancy (Onyeneko et al., 2016).

Inadequate nutrition may be another risk factor for prematurity, LBW, or pregnancy loss, especially in teenaged pregnancy or for women at risk for not eating due to food insufficiency or conditions such as anorexia nervosa or depression. Many teenaged girls do not eat an adequate diet, even when they may not be pregnant. They may not consume adequate trace elements or antioxidant micronutrients in their diet (i.e., selenium, copper, zinc, manganese, and vitamins C and E) during pregnancy, which are essential in the promotion of adequate placental development, prevention of FGR, and prevention of fetal mortality and morbidity (Micali, Stemann-Larsen, Strandberg-Larsen, & Nybo Anderson, 2016). Young mothers who do not consume enough nutrients to maintain their own growth, as measured by gains in BMI or height, are more at risk to have LBW infants compared to older mothers. Both high and low maternal BMI have been associated with poor pregnancy outcomes for both mother and neonate. Obesity rates have been steadily increasing in industrialized nations with the result of decreased fertility, increased miscarriage when pregnancy is achieved, and increased risk of preeclampsia (Broughton & Moley, 2017; Kim et al., 2016). In response to the risks of poor pregnancy outcomes while obese, many women of childbearing age have chosen bariatric surgery for weight reduction prior to conception. While undergoing this procedure has decreased risk of complications associated with obesity, there is the increased possibility of complications related to poor nutritional intake due to malabsorption of micronutrients needed to support healthy pregnancy and normal fetal growth (Carreau, Nadeau, Marceau, Marceau, & Weisnagel, 2017; Chevrot et al., 2016; Jans et al., 2015).

Conditions in many countries contribute to chronic undernutrition throughout the life span resulting in poor pregnancy outcomes. Girls are more at risk for nutritional deprivation in some countries due to girl gender bias. Chronic undernutrition can delay menarche in young girls. In some cultures, especially rural, underdeveloped populations, early adolescent marriage and pregnancy are permissible. In a study conducted in India where many pregnant women experience chronic undernutrition, adolescent girls less than age 18 with low BMI of less than 18.5 kg/m^2 were found to be at increased risk for pregnancy wastage and prematurity compared with those older than 18 with low BMI. Additionally, prematurity rates were significantly higher in girls who married prior to age 18 compared with those who married after age 18. Pregnancy wastage was six times higher in mothers who conceived at less than 15.25 years compared with those who conceived after 17.25 years. Adolescent pregnancy outcomes often include maternal anemia and preterm delivery (Kawakita et al., 2016). Food insecurity not only can increase risk for a LBW infant but can increase risks of birth defects. Food insecurity can also lead to changes in maternal mental health, including depression, anxiety, and low self-esteem (Pellowski et al., 2017). Interventions that can help improve nutritional status of pregnant women in food-insecure locations are also aimed at increasing infant birth weight, which can markedly decrease infant mortality. Effective interventions include maternal supplementation with iron folate and micronutrients, calcium supplementation, iodized salt, reduction in indoor pollution and tobacco usage, intermittent preventative treatment for malaria, and use of insecticide-treated mosquito nets (Cox et al., 2018; Wallace et al., 2017; WHO, 2016b).

Even in high- to moderate-income nations, some pregnant women living on low incomes do not get adequate nutrition. In the United States, nutritional support during pregnancy along with nutritional education, and participation in programs such as the Special Supplemental Nutrition Program for Women, Infants, and Children (SNAP), have been demonstrated to increase the mean birth weight and reduce the odds for LBW for infants of low-income women on Medicaid. The use of foodbanks is increasing in middle and higher income countries as food insecurity

increases in rural as well as urban areas as families face the challenges of meeting multiple monetary and social needs (Chang, Kim, & Chatterjee, 2017; Loopstra, 2018). Unfortunately, the use of the SNAP program and foodbanks as a nutrition resource has not improved the nutritional intake of pregnant women as expected due to the availability of primarily processed foods with low nutritional value. Availability of fresh fruits and vegetables is costly and still limited, especially in more urban areas (Mulik & Haynes-Maslow, 2017; Spees, Clark, Hooha, Watowicz, & Taylor, 2017). One result of the lack of available nutrient-rich food is continued maternal obesity among participants of the SNAP program (Sanjeevi, Freeland-Graves, & Hersh, 2018).

Maternal foodborne illness or ingestion of toxic substances during pregnancy can be harmful to the fetus. *Listeria monocytogenes,* even though rare, is a special concern in pregnancy since pregnant women have a 10 times greater risk of becoming infected (CDC, n.d.-c). Women who ingest food contaminated with *Listeria* do not usually feel ill; however, the fetus can be significantly affected. Eating food contaminated by microorganisms like *Listeria* or substances like heavy metals can cause abortion, stillbirth, preterm delivery, neonatal infections, fetal brain or kidney problems, or even maternal death. While *Listeria* is found in many foods, teaching pregnant women simple basic precautions such as handwashing when preparing food, avoiding cross-contamination of meat dishes or other prepared foods, and avoiding nonpasteurized milk may help prevent infection (McNeill, Sisson, & Jarrett, 2017).

Pica is an interesting dietary practice seen during pregnancy in almost every culture. Substances like starch, ice, clay, or dirt are ingested as a craving in an attempt to possibly increase iron or calcium intake. The harmfulness of pica in pregnancy is dependent on the substance and amount ingested by the pregnant woman. Women who practice pica tend to have lower hemoglobin and hematocrit levels and be more underweight at the start of their pregnancy (Epler, Pierce, & Rappaport, 2017). One concern if the mother eats dirt or paint chips is that it could possibly be contaminated with lead or heavy metals which could be harmful, cause anemia, or result in lead poisoning. Contamination of soil and water increases the risk of elevated lead levels in women, which can then result in increases in spontaneous abortion, fetal deaths, or infants with LBW (Hanna-Attisha, LaChance, Sadler, & Schnepp, 2016; Tian, 2017).

The influence of cultural dietary practices as potential risk factors can't be ignored and must be assessed. Asian women who ingest betel nuts, which contain arecoline, are at higher risk for spontaneous abortion, LBW, and PTB, placental changes, and neonatal withdrawal (Berger et al., 2016). Some populations continue to use lead-glazed ceramic ware and traditional folk remedies that are lead-based even after immigration into the United States (Welton, Rodriguez-Lainz, Loza, Brodine, & Fraga, 2016). The healthcare practitioner must become familiar with the food and complementary medicine cultural practices of local ethnic groups, as they may affect pregnancy outcomes.

Over-the-Counter and Complementary Drugs

Drugs taken during pregnancy can have harmful effects on the fetus whether they are controlled substances or over-the-counter medications. Despite warnings that pregnant women should not take any medications without consulting with their healthcare provider, many pregnant women take over-the-counter or nonprescribed medications during pregnancy, including complementary therapies they might not consider to be harmful. Findings of a study by Haas et al. (2018) on the prevalence of medication use by nulliparous pregnant women reported that 97.1% of women used one or more medication during their pregnancy. About 95.7% said they used at least one prescription or over-the-counter medication in the first trimester of pregnancy. Prescribed antidepressants and asthma medications are among the most commonly prescribed used during pregnancy. Many women regularly take over-the-counter drugs such as cold remedies, aspirin, nonsteroidal anti-inflammatory drugs, or herbal teas. Some women might take medications that could be harmful to the fetus before they know that they are pregnant. Even vitamins and dietary supplements taken in excessive dosages can be harmful to the fetus. Pregnant women with preexisting medical problems such as asthma, arthritis, heart problems, diabetes, or epilepsy who have to continue to take their prescribed medications during pregnancy should check with their healthcare provider to determine if the prescribed medication will need to be changed to one that is less harmful to the fetus. Communication between patient and provider is essential as some women stop taking their prescribed medications when they cannot access information stating there is no risk to the fetus (Lynch et al., 2017; Sinclair, Lagan, Dolk, & McCullough, 2018).

Healthcare providers must be cognizant of Food and Drug Administration (FDA) pregnancy categories and drugs that must be used with caution or that are contraindicated in pregnancy. Thalidomide was withdrawn from the market in the 1960s after it was linked to fetal limb shortening birth defects when it was used during pregnancy. Currently, thalidomide is being used to treat chronic multifocal osteomyelitis and chronic granulomatous disease (Martin-Nalda et al., 2016). Both are rare conditions but can occur in women of childbearing age. Thalidomide analog medications have been developed, which have lesser teratogenic effects and are used to treat psoriasis (Rosenberg & Meyerle, 2017). There are stringent educational requirements, warnings about risks in pregnancy, and mandatory contraception for both men and women who use thalidomide. It is possible that pregnancy could occur despite these measures.

Environmental Influences

Every individual is conceived with a unique genetic makeup called a genotype. The phenotype, or the person's ultimate physiological and psychological makeup, is determined during the postconceptual period until after birth. The expression of the genetic inheritance (i.e., actual physiological and psychological makeup of the person) is the result of complex gene–gene interactions and environmental influences upon genes that occur at the molecular level. Exposure by the mother to environmental toxicants either before or during pregnancy can precipitate gene–environment interactions that can alter these molecular interactions, especially if the exposure to the harmful substance occurs at critical periods of fetal development. Two critical periods when gene–environmental interactions can be most harmful are during organogenesis (when fetal organs are being formed) and during the fetal period when there is rapid growth of all systems. Spina bifida is an example of a gene–environment interaction. At conception, a fertilized egg might inherit the genes to have an intact neural tube. Neural tube defects occur when there is a lack of adequate folic acid at a critical stage of development while in utero. Exposure to teratogens, substances that are known to cause birth defects, during these times can result in birth defects or other adverse outcomes. Two pregnant women could be exposed to the same toxicants at the same point during pregnancy and could have infants with different outcomes. For example, two infants could inherit the genetic trait for sickle cell disease, yet when they are born they could have different expressions of the disease based upon other complex molecular interactions that happen within genes, which could be influenced by

the environment. It is now recognized that these factors continue to influence functional and developmental outcomes throughout the person's life (Singh, Miaskowski, Dhruva, Flowers, & Kober, 2018). The study of epigenetics is an evolving science that looks at factors such as genetic inheritance, imprinting, or nutritional factors that are hypothesized to mediate genetic interactions at the molecular level and that may one day provide more insight into these complex processes.

Environmental hazards are found in air, water, and food. Environmental changes have increased health risks related to increases in air pollution, water contamination, and the impact of extreme weather events (Nicholas & Breaky, 2017). Maternal exposure to air pollutants during weeks 16 to 18 of pregnancy has been associated with decreased fetal birth weight (Warren, Son, Pereira, Leaderer, & Bell, 2018). Exposure to increased particulate matter in the air during natural geologic events, such as dust storms and volcanic eruptions, has been associated with increases in PTB and LBW (Altindag, Baek, & Mocan, 2017; Balsa, Caffera, & Bloomfield, 2016). Poor or socially disadvantaged women, especially women of color, are more often exposed to environmental hazards because they tend to live in older sections of towns or work in areas with high exposure. Their homes are usually older, increasing the risk for lead paint exposure. Poor parts of towns are often located close to factories where pregnant women are exposed to incinerator emissions or other sources of air pollution. Air pollution exposure in the third trimester has been associated with preterm labor (Li, Guo, & Williams, 2016). Fine particulate air pollution such as that produced by passive exposure to cigarette smoke, organic pollutants, and motor vehicles can have detrimental effects on pregnancy outcome and early childhood health concerns related to lung development and fetal size (Janssen et al., 2017; Korten, Ramsey, & Latzin, 2017). Urban populations with intensified motor vehicle traffic are areas where prenatal and perinatal exposure to air pollution have informed findings of increased asthma and eczema in children (C. Lee et al., 2017; Alison Lee et al., 2018).

Suburban and rural populations are more likely to be exposed to agricultural pesticides or chemicals as they are more likely to garden and do yardwork. Another population at risk for pesticide and chemical exposure are those who work on farms or as migrant workers. Both maternal and paternal exposure to environmental toxins can be contributors to fetal risk and result in alterations in neurodevelopment and IQ (Gunier, Bradman, Harley, Kogut, & Eskenazi, 2017; Liu et al., 2016; Sagiv et al., 2018). The disadvantaged might be more likely to reside on or near land that once served as a hazardous waste dumpsite (Anetor, 2016). Birth outcomes can also be affected by the occurrence of natural or man-made disasters such as hurricanes, severe ice storms, earthquakes, chemical spills, or terrorism. The occurrence of a disaster can alter availability of safe food and water, or adequate prenatal care, which may increase risks for PTB. Increased maternal stress could cause mothers to use substances such as alcohol or tobacco for stress management. There have been some studies linking certain disasters with outcomes such as increased rates of spontaneous abortion, congenital anomalies, decreased fetal growth, and changes in maternal mental health status, although disasters do not seem to cause PTB.

Emerging Risk Factors

Sleep problems during pregnancy have been linked to an increased risk for FGR or LBW and assisted delivery (Plancoulaine et al., 2017). Preterm delivery was more common among women receiving the least amount of sleep prior to pregnancy who obtained lessening hours of sleep as pregnancy progressed. Sleep-disordered breathing is a term applied to multiple types of sleep disturbances. This term can mean anything from snoring to obstructive sleep apnea. Obstructive sleep apnea in pregnancy may be the consequence of comorbidities of pregnancy such as obesity, smoking, and race. Maternal obstructive sleep apnea is associated with increased frequency of preterm, SGA infants who require NICU admission (Felder, Baer, Rand, Jelliffe-Pawlowski, & Prather, 2017; Louis, 2018).

MATERNAL MEDICAL AND OBSTETRIC CONDITIONS

Diabetes, hypertension, and bleeding disorders are some of the most common maternal complications of pregnancy. These complications can lead to preterm delivery, perinatal death, or can influence fetal morbidity. WHO (2018c) has identified severe bleeding after childbirth, infections after childbirth, and hypertension as three of the major causes of maternal mortality worldwide. Recommendations for antenatal care include assessment for anemia, asymptomatic bacteriuria, and intimate partner violence (WHO, 2016b). The risk of maternal complications of pregnancy increases with advanced maternal age (AWHONN, n.d.; Fitzpatrick et al., 2016).

Diabetes

Women with known pregestational diabetes should seek preconceptual care prior to getting pregnant. The preconceptual visit should include a complete physical examination with evaluation of blood glucose levels, cardiovascular and renal health, gastrointestinal system, an eye examination to check for diabetic retinopathy, and evaluation of the presence of neuropathy. A team approach with a diabetes nurse educator and dietician can teach the woman how to implement the dietary and lifestyle changes needed for a healthy pregnancy. Oral hypoglycemic medication may be continued in pregnancy with monitoring of maternal glucose levels. Metformin can be used safely in the preconceptual period and during pregnancy for type 2 diabetics (Romero et al., 2017). Metformin in combination with glyburide during pregnancy reduced the need for insulin (Nachum et al., 2017). Ideally, the woman with diabetes should maintain euglycemia for several months prior to pregnancy, as hyperglycemia in early pregnancy has been associated with increased risk for pregnancy loss and serious congenital defects (Waters et al., 2016). During pregnancy, regulation of blood glucose is sometimes difficult since pregnancy creates a state of insulin resistance and insulin needs change with each trimester. Glycosylated hemoglobin (HbA1c) levels should be maintained to as close to normal range as possible during pregnancy, especially during the period of fetal organogenesis.

Adoption of the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria has resulted in increasing the identification of gestational diabetes (Trujillo et al., 2015). Worldwide prevalence of gestational diabetes mellitus (GDM) is difficult to establish. Currently, research is being undertaken utilizing the IADPSG and WHO (2013) criteria to better assess and intervene with diverse populations (Hagiwara et al., 2018; Tan et al., 2017; Wong, Lin, & Russell, 2017). In the United States, there are ethnic variations in the prevalence of GDM, with Asian, Hispanic, and Native American women having higher rates than NHB and NHW women. Identification and treatment of women with gestational diabetes is the key to promoting positive neonatal outcomes. The most important principle of diabetes management for all pregnant women with diabetes is to maintain tight glycemic control. Poor glycemic control increases the risks for birth defects (i.e., cardiovascular, musculoskeletal, and central nervous system

anomalies), hypoglycemia, respiratory complications, and shoulder dystocia (Babović, Arandjelović, Plešinac, Kontic-Vučenić, & Radunović, 2018; Barquiel et al., 2016; Khambalia et al., 2017; Yamamoto, Kallas-Koeman, Butalia, Lodha, & Donovan, 2017).

Currently, pregnant women in the United States are screened for gestational diabetes following review of patient history, presence of clinical risk factors, and administration of a 50-g 1-hour oral glucose tolerance test (OGTT). If positive, a second step 100-g 3-hour OGTT follows. The American Diabetes Association (ADA) recommends a 75-g OGTT at 24 to 28 weeks with blood glucose measurement when fasting, and at 1 and 2 hours after blood glucose administration. The diagnosis of gestational diabetes is based upon results of the blood glucose screening which exceed predetermined laboratory values for the test. Current WHO (2013) recommendations follow the IADPSG guidelines.

Diabetes during pregnancy is frequently accompanied by maternal vascular changes that can compromise uteroplacental circulation; therefore, fetal nonstress testing is recommended in the last trimester. If early delivery is indicated, amniocentesis can be done to determine fetal lung maturity; however, results of the lecithin sphingomyelin (L/S) ratio are often inaccurate for infants of mothers with diabetes. Infants of diabetic mothers generally have macrosomia. These large babies have increased risks for birth injuries due to shoulder dystocia, including fractured clavicles or nerve palsies. Large infants are more likely to be delivered by cesarean section. Infants of diabetic mothers should be closely monitored for hypoglycemia in the immediate postbirth period and until feeding is well established.

Hypertension in Pregnancy

Approximately 6% to 8% of pregnancies are complicated by hypertensive disorders. The four identified categories of hypertension in pregnancy are: chronic hypertension, gestational hypertension, preeclampsia, and preeclampsia superimposed on chronic hypertension (Folk, 2018). Chronic hypertension exists when there is a history of hypertension prior to the pregnancy, or it can also be diagnosed during pregnancy for the first time. Some women with preexisting hypertension develop superimposed preeclampsia during their pregnancy (Nzelu, Dumitrascu-Biris, Nicolaides, & Kametas, 2018). Women with chronic hypertension who develop superimposed preeclampsia are at increased risk for fetal complications (Folk, 2018; Nzelu et al., 2018). Gestational hypertension is diagnosed during pregnancy and usually disappears within 12 weeks after delivery. Preeclampsia is a pregnancy-specific disease that usually occurs after 20 weeks of pregnancy. It is characterized by hypertension, thrombocytopenia, and signs of renal impairment (Nzelu et al., 2018). As the condition progressively worsens, maternal laboratory work indicates elevations in liver enzymes and low platelets. HELLP (hemolysis, elevated liver enzyme levels, and low platelet levels) syndrome occurs in about 20% of pregnancies complicated by preeclampsia. It is characterized by hemolysis, elevated liver enzymes, and low platelets. Approximately half of women with *HELLP* syndrome are preterm.

Hypertension in pregnancy causes vasoconstriction with subsequent poor maternal circulatory and placental perfusion. Decreased uteroplacental circulation compromises the fetus; therefore, it is more likely to be growth restricted, SGA, or at increased risk for stillbirth (Heider, 2017). Women with gestational hypertension are also at increased risk for abruptio placenta. Delivery is the definitive treatment and is generally recommended if the fetus is 34 weeks' gestation or more; however, it might not be appropriate if the fetus is immature (Sievert et al., 2017). Early delivery will be based upon stability of the mother and outcomes of fetal testing. A serious risk for the preeclamptic mother is the possibility of eclamptic seizures due to cerebral edema and central nervous system excitability or progression to the HELLP syndrome. Seizures increase the risk for a placental abruption. Therefore, if the mother's condition worsens, early delivery will be elected; however, the ability of the fetus to survive must be considered (Kuper, Sievert, Biggio, Tita, & Harper, 2017). Corticosteroid administration is advised and may be beneficial if the fetus is between 24 and 34 weeks of gestational age and if the mother has never had them (Travers et al., 2018). Patients with preeclampsia tend to have infants with lower gestational ages at delivery and lower birth weights than do patients with gestational hypertension alone (Kuper et al., 2017; Sievert et al., 2017). Women with severe gestational hypertension (defined as blood pressure >160/110) without proteinuria can quickly develop severe complications of preeclampsia such as thrombocytopenia and pulmonary edema effecting neonatal outcomes (Folk, 2018). The earlier that hypertensive disease occurs in pregnancy, the more likely it is that complications will develop reinforcing the need for early and consistent prenatal care (Sonek et al., 2018).

If preeclampsia worsens, the pregnant woman is admitted to the hospital for stabilization and delivery. If the woman has a seizure, oxygen should be provided during and immediately following the seizure and the fetus should be monitored for signs of distress. Magnesium sulfate is the drug of choice to prevent central nervous system excitability from cerebral edema. Infants rarely have harmful effects from in utero exposure to magnesium sulfate prior to delivery but should be monitored for signs of respiratory depression or hypotonia after birth.

Ethnic differences in the progression of hypertensive disorders in pregnancy have been noted. African American women were hospitalized earlier in the pregnancy for treatment of gestational hypertension. Their babies had lower gestational age and birth weight. African American women also had a higher incidence of abruptio placenta, stillbirths, and neonatal deaths than other ethnic groups despite starting prenatal care in the first trimester (Hoyert & Gregory, 2016; Martin et al., 2018).

Prelabor Rupture of Membranes

PROM is a cause of preterm delivery and can occur at any time during a pregnancy. Following rupture of membranes, the fetus is at increased risk for problems related to oligohydramnios, cord compression, chorioamnionitis, and abruptio placenta. Women with PROM may report that they are leaking fluid from the vagina or may have experienced a gush of fluid. Sterile speculum examination, nitrazine testing, and microscopic examination of fluid for ferning are methods to evaluate if membranes have ruptured. The decision of whether to deliver or to use expectant management must weigh the advantage of postponing delivery until gestational age increases against the risk for maternal or fetal sepsis. Current ACOG guidelines recommend expectant management when premature prelabor rupture of membranes (PPROM) occurs at less than 34 weeks if no maternal or fetal contraindications are present (Ehsanipoor, 2018). When PPROM occurs between 24 and 34 weeks' gestation, a single course of corticosteroids is recommended. PPROM prior to 32 weeks, which exhibits signs of possible delivery, should be treated with magnesium sulfate for the neuroprotective effect on the neonate. A course of antibiotics may also be considered to prevent infection. Signs of intrauterine infection include fever greater than 100.4°F (38.0°C), uterine tenderness, and maternal or fetal tachycardia. Results of the white blood cell count tests should be used judiciously as an indicator of infection, especially if steroids have been given within the previous 5 to 7 days.

Fetal outcomes after PPROM are related to gestational age at time of membrane rupture and whether the infant is delivered without complications of infection or asphyxia from cord compression or prolapse. Neonates born at 22 weeks' gestation after PPROM have lower survival rates. As gestational age increases from 23 to 32 weeks' gestation, outcomes after PPROM improve. Preterm PROM near term occurs between 32 and 36 weeks' gestation, and infants who are delivered at this time are more likely to survive if they do not have other complications (Stensvold et al., 2017). Sometimes in the absence of other indications, a wait and see approach might be taken where delivery is not expedited. If PROM occurs at earlier gestational ages, the risk for chorioamnionitis increases. At delivery, infants of women with chorioamnionitis tend to be of younger gestational age and to weigh less than infants of women who do not have chorioamnionitis. However, research has demonstrated less risk of neonatal sepsis with increased time interval between PPROM and delivery (Lorthe et al., 2017).

Maternal Infections

Infections are a major risk factor for maternal and fetal health during pregnancy. Women may be infected prior to pregnancy or acquire the infection during pregnancy. Maternal infections can be transmitted to the infant while in utero across the placenta, during the birth process, or even during the postpartum period. Fetal infections can cause congenital anomalies, LBW, respiratory illness after birth, or even death. Infectious agents include protozoal infections, helminthic infections, sexually transmitted infections (STIs), viruses, and bacterial organisms.

Three infectious diseases, HIV/AIDS, tuberculosis (TB), and malaria, are the leading causes of perinatal morbidity and mortality, especially in sub-Saharan Africa and Asia. Interactions between these diseases during pregnancy can increase maternal risk of contracting other infectious diseases or can potentiate the existing diseases, increasing morbidity and mortality. For example, malaria and TB infections can increase the risk of vertical transmission of HIV to the fetus. The presence of maternal HIV infection can decrease maternal immunity, lowering resistance to TB or malaria (Natureeba et al., 2017). TB-infected women are more at risk to contract malaria or HIV. Tragically, many of these deaths could be prevented through use of low-cost interventions to prevent vertical transmission of HIV, intermittent prophylactic therapy, use of insecticide-treated nets for malaria prevention, and infection control practices for TB (Natureeba et al., 2017). The most current WHO (2016b) recommendations for antenatal care include intermittent treatment for malaria prevention in endemic areas and HIV prophylaxis to women at high risk.

Vaccine-preventable infections kill more women and babies in low-income nations because basic immunization practices, such as tetanus or rubella vaccination, may be unavailable to them. Tetanus, a disease that can be easily prevented, still accounts for neonatal deaths in developing nations. Although WHO (2016b) recommendations include immunization, lack of knowledge regarding the disease and neonatal mortality prevent some pregnant women from receiving the vaccine (Shafiq et al., 2017). Tetanus develops in newborns due to unclean cord-handling practices, including instrumentation and use of traditional cord salves that can cause infection. Once infected, the infant loses the ability to suck within a few days of exposure and progresses through stiffness, seizures, and death (WHO, 2018b). Rubella in pregnancy can result in miscarriages, stillbirths, or severe defects in the surviving fetus. Congenital rubella syndrome persists in some countries where vaccination is not available or not a standard of care for pregnant women (Herini et al., 2017). Symptoms may include hearing impairment, congenital cataracts, microcephaly, and congenital heart defects.

An additional infectious, mosquito-borne illness has presented in rural, suburban, and urban areas of several countries. In 2015, the link between Zika virus (ZIKV) contracted during pregnancy and microcephaly was announced by the Ministry of Health in Brazil following examination of data regarding an increase in microcephaly occurrence in that country (De Carvalho, De Carvalho, Fugaça, Dóris, & Biscais, 2016). Human infection with ZIKV had already been seen in other subtropical and tropical islands and countries with the same outcomes. Since the recognition of the ZIKV in pregnancy as teratogenic, the virus has been identified as a cause of additional abnormalities such as brain malformation, eye abnormalities, and some central nervous system disorders (Fitzgerald, Boyle, & Honein, 2018). Unfortunately, many of those infected are asymptomatic or mistake the flu-like symptoms as a minor ailment. Testing is currently recommended for women who travel to known areas where the vector mosquito survives (Eppes et al., 2017); however, the virus can also be transmitted through intercourse and perinatally. Prevention measures advised include topical insect repellent sprays and long clothing (De Carvalho et al., 2016). Prevention of sexually transmitted ZIKV may be more challenging as the carrier would have to be identified and willing to use barrier methods of birth control (Santibañez et al., 2017).

SDG 3 focuses on combatting HIV/AIDS, malaria, TB, and other infectious diseases and on the prevention and treatment before and during pregnancy of infectious and noncommunicable diseases known to increase the risk of PTB (United Nations, 2015). Every pregnant woman must be screened for risk factors for infection. Early identification and treatment of women with infections will improve both maternal and neonatal outcomes.

Abruptio Placenta

Abruptio placenta, or premature separation of the placenta prior to delivery, is a leading cause of stillbirth and neonatal mortality. Placental separation is thought to be due to changes in placental vasculature, thrombosis, and reduced placental perfusion. A genetic basis for abruptio placenta has been speculated as the cause for these changes. Placental separation occurs in several ways. In marginal separation, the edges of the placenta separate and bright red bleeding is present. Occult or hidden abruptio placenta occurs when the edges of the placenta are intact but the central part of the placenta detaches from the uterus, allowing blood loss to accumulate behind the placenta without any outward signs of bleeding. Complete abruptio placenta occurs when the placenta totally detaches, a situation that is incompatible with fetal survival. There is a four to six times higher risk of premature delivery when there is a diagnosis of abruptio placenta. Premature delivery increases the risk for infant mortality. Risk of mortality due to abruptio placenta is higher than when abruptio placenta is not present (Downes, Shenassa, & Grantz, 2017). **Quality & Safety: Infants of mothers with abruptio placenta who survive must be closely monitored for signs of blood loss and shock.**

Risk factors for abruptio placenta include smoking, multiple pregnancy, and maternal age greater than 50. Increased risk in older women could be related to increased rates of chronic hypertensive disorders or aging of the uterine blood vessels. The risk of abruptio placenta increases with multiple pregnancy as the number of fetuses increases from singleton to triplet pregnancies. The risk of perinatal complications such as preterm delivery, intraventricular hemorrhage, and death increases in the presence of abruptio placenta (Chevallier et al., 2017).

POSTPARTUM RISK FACTORS

After birth, the leading causes of infant death are congenital anomalies, complications of prematurity and LBW, SIDS, and perinatal complications (Murphy et al., 2017). Congenital anomalies account for most neonatal deaths in the first month of life. Infants who are LBW are more likely to die from complications of prematurity (respiratory distress, infections, or anemia), maternal complications in pregnancy, or placenta/cord conditions. In addition to these leading causes of death, other risk factors such as maternal smoking or drug usage could affect the health of the neonate or cause injury. Providing information and anticipatory guidance to the parents to increase awareness of some of these factors might be enough to protect the infant and to promote positive outcomes.

Drugs Excreted in Maternal Milk

Maternal medications taken while lactating is a concern as medications may alter the milk supply or cross to the infant though the milk supply. While many medications have been demonstrated to be safe, there are still others that have not been reported in the literature. Psychotropic drugs pose a special concern since there has been an increase in their use. These drugs and their metabolites have long half-lives and are detectable in infant tissues and the developing brain. The long-term consequences of this exposure have not been thoroughly studied. As new drugs are placed on the market, their safety for the infant must be evaluated. Some untoward effects on the infant from use of prescribed maternal drugs include possible immune suppression, neutropenia, skin rash, central nervous system changes including irritability, restlessness, sleepiness, lethargy, or convulsions, and gastrointestinal effects such as feeding problems, vomiting, diarrhea, slow weight gain, blood in stool, jaundice, or dark urine. A comprehensive list of drugs, foods, and environmental agents that are excreted in human milk and that could be potentially harmful to neonates is available from the American Academy of Pediatrics (AAP).

The AAP recommendations include the use of the LactMed app provided by the National Institutes of Health (NIH, n.d.a), as a resource for current toxicology and information on medications of any kind. The app is free and downloadable to multiple devices and can be used by professionals as well as the general public. Medication information is updated monthly. When drugs are prescribed for lactating women, the following factors should be considered. When a medication is absolutely necessary, the baby's pediatrician and mother's physician should consult together to select the most appropriate drug for the mother, with minimal effects upon lactation and minimal transfer to the infant. Select the safest drug when there are several to choose from. Consider measuring the infant's blood concentration of the drug if there are potential risks from the drug for the infant. Advise the nursing mother to take the medication immediately after breastfeeding the infant or after a feeding that will be followed by an expected infant sleep period, to minimize infant drug exposure.

Sudden Unexpected Infant Death Syndrome

Sudden unexpected infant death syndrome (SUIDS) is a leading cause of death in infants in the postneonatal period in the United States as well as in other developed countries. SUIDS is broken down into SIDS, unexplained deaths, and accidental strangulation/suffocation in bed. Programs such as the AAP Back to Sleep campaign urged parents to place their infants on their backs instead of prone for sleeping. This change in recommended practice dramatically lowered infant deaths from SIDS. In the United States, the SIDS death rate declined between 1990 and 2015, from 130.3 to 39.4 per 100,000 live births (CDC, n.d.-d). Despite these advances, disparities in SIDS rates exist. Infants born to Black or American Indian or Alaskan Native mothers have the highest rates of death from SIDS at twice the rate of infants of White mothers. Infants of Hispanic and Asian or Pacific Islander mothers have the lowest rates (CDC, n.d.-d). Maternal risk factors include young, single mothers with a history of prenatal smoking or substance abuse. Infant mortality has decreased in the United States with improvements in prenatal care through Medicaid expansion and public health programs aimed at educating the consumer regarding early delivery, smoking, and safe sleep habits (Bhatt & Beck-Sagué, 2018; Hirai et al., 2018).

Over 70 causes of SIDS have been proposed. SIDS has been blamed on environmental factors such as soft bedding, overheating, entanglement in blankets, immunizations, tobacco smoke exposure, or bed sharing with parents or siblings, especially if a bed partner consumes alcohol (Spinelli, Collins-Priano, Van Den Heuvel, & Byard, 2017). Genetic factors have also been blamed for findings. Possible structural defects in the brain that control cardiac and respiratory function might explain the diminished arousal response in infants with SIDS that precedes death. Cardiac mutations resulting in long QT syndrome have been identified in 5% to 10% of SIDS victims (Moon, 2016). In reality, the cause of SIDS is probably multifactorial. The triple risk theory proposes that multiple complex factors (including genetics, prenatal risk factors, and environmental risk factors) make some babies more vulnerable to environmental triggering events and unable to respond to these events through usual homeostatic mechanisms (Moon, 2016; Spinelli et al., 2017). Preterm or LBW infants are at increased risk for SIDS (Ostfeld, Schwartz-Soicher, Reichman, Teitler, & Hegyi, 2017). Term infants with a history of apnea are also at risk. The peak age at death from SIDS is between 1 and 4 months with the majority of deaths occurring before 6 months of age (NIH, n.d.b). No definitive link between SIDS and immunizations has been established.

Sleeping in the prone position has been highly associated with SIDS and is one reason the Back to Sleep campaign has been so successful in reducing SIDS death rates. The rate of SIDS increases for preterm infants who are placed in the prone position. Many parents of premature infants place their infant to sleep on his or her stomach or side once at home. It is possible that new parents are learning the practice of putting their baby in either the prone position or sidelying position by watching caregivers in the NICU. Neonatal care practices that place preterm infants in the prone or sidelying positions are providing poor role models for parents. Every time parents see their baby in a prone or sidelying position while in the hospital, they are getting reinforcement of a poor practice about how to provide care to their baby at home. Infants become habituated to the prone position for sleeping, especially if they have had a prolonged hospitalization, which makes it more difficult for parents to change the baby's sleeping position to the back-lying position. Nurses need to educate parents and encourage them to share information with their childcare providers about placing the baby on the back to sleep (Dufer & Godfrey, 2017). Neonatal nurses must continue to educate each parent about the risk factors for SIDS and remind parents that the safest place for a baby is in its own crib in the parents' room for the first 6 months.

Child Abuse

Child abuse in infants is sometimes difficult to identify. Parents of an injured infant arrive for emergency treatment and seem severely distraught and worried about their child's injuries. They often

offer reasonable explanations for the injury that must be ruled out with medical tests. The victims, the babies, can't speak for themselves to describe what happened. New parents are subject to many stressors that could trigger child abuse such as lack of sleep, financial strain, and dealing with inconsolable infants. Healthcare providers have a legal and ethical duty to report cases of suspected child abuse to child protective services (Ho, Bettencourt, & Gross, 2017). Two forms of child abuse are discussed further: abusive head trauma (AHT), a subset of shaken baby syndrome (SBS), and Munchausen syndrome by proxy (MSBP).

Abusive Head Trauma/Shaken Baby Syndrome

AHT describes a serious form of head trauma caused by several mechanisms including abusive shaking of an infant causing a whiplash-type injury, blunt trauma, or a combination of both (Miller Ferguson et al., 2017). It is a public health issue and the leading cause of death due to child abuse. When the infant is shaken, the head flops back and forth causing rapid acceleration, deceleration, and/or rotational forces of the brain within the skull, causing stretching, shearing, and tearing of blood vessels of the brain. Several types of injuries occur with AHT/SBS. Intracranial injuries cause direct brain injury and damage to the axons. Shearing forces exerted on the veins that bridge from the dura to the brain cause intracranial bleeding. During shaking, there is a lack of oxygen to the brain that is further compounded by chemical processes that occur within the damaged cells. These injuries lead to swelling of the brain and increased intracranial pressure that further compromises brain oxygenation. Even 1 year after injury, children with AHT may have retinal hemorrhages, seizures, and signs of other injuries. External signs of injury to the face or head may be present as well as injuries or bruising of the long bones, thorax, or abdomen may occur as a result of firmly grasping the infant during the shaking episode (Miller-Ferguson et al., 2017).

AHT/SBS most often results when a parent becomes frustrated with an infant who is crying and inconsolable. Parents who are stressed with the parenting role, parents of premature infants, those who are sleep deprived, or parents who do not have support or help to care for their baby's needs may have low tolerance of infant crying. Poverty and stress are risk factors for abuse. In frustration they may pick up the baby and shake it to try to quiet the baby. Newborns are more susceptible to the forces of shaking and may sustain injury even if not shaken as roughly as an older child. Once parents shake their child and get a response, they might shake the child again over time, causing the infant to be injured repeatedly. Because the intracranial bleeding can be slow initially, the child might not manifest symptoms until 48 to 72 hours after the injury. Children who appear to have mild injury may not be brought to the hospital by parents immediately and be misdiagnosed by healthcare providers (Christian; AAP Committee on Child Abuse and Neglect, & AAP Section on Child Abuse and Neglect, 2015).

When parents seek medical attention for the infant, the history of events that preceded the infant's symptoms is often vague. Signs of AHT/SBS vary based on the extent of the injury and are sometimes subtle such as feeding difficulties, vomiting, lethargy, hypothermia, failure to thrive, and increased somnolence. More life-threatening signs include seizures, bulging fontanelle, apnea, coma, bradycardia, or complete cardiovascular collapse. Outcomes are poor for children who present with coma. Survivors of coma may have severe neuromotor impairment, visual impairment, and developmental delay. They may require shunting for hydrocephalus. Long-term occupational therapy, physical therapy, and speech therapy will be needed to help the children achieve their maximum potential. Approximately 20% of infants might die as a result of the shaking abuse. A small percentage of children will have no outward ill effects from the shaking. The remaining children have long-term sequelae, including ongoing neurological injuries and visual impairment.

New parents need to be taught not to shake their infant at any time. Prior to discharge, time should be spent exploring parents' concerns about taking a newborn home, their sources of support, and their coping strategies under stress. Teach parents about normal infant crying patterns and how to handle their stress or frustration due to prolonged periods of infant crying (Kelly et al., 2017). Referral for stress management techniques, anger management, and provision of a parenting hotline number might help prevent this devastating injury. Hospital-based education programs have been effective in reducing the occurrence of AHT/SBS in the high-risk neonatal populations (Lopez-Bushnell, Torrez, Robertson, Torrez, & Strickler, 2017).

Munchausen Syndrome by Proxy

MSBP is a rare form of child abuse where a parent, usually a mother, fabricates illness in a dependent child in order to draw attention to themselves as the parent of a sick child. Four criteria are required for a diagnosis: (a) a parent or guardian fabricates illness in the child, (b) the child is presented for medical care, (c) the perpetrator denies knowledge of the cause of the child's illness, and (d) the signs and symptoms subside if the child is separated from the perpetrator (Gehlawat, Gehlawat, Singh, & Gupta, 2015). The diagnosis of MSBP includes two diagnoses: one for the child and one for the parent. The parent response might range from fabricating illness of a child, exaggerating symptoms of the sick child, to actually inducing the symptoms in the child such as by attempts to suffocate or poison the child. Some of the most common types of fabrications include gastrointestinal (diarrhea), neurologic (seizures), infections (fevers), dermatologic (strange rashes), and cardiopulmonary (acute life-threatening events). Some children will die as a result of the parent's abuse or ministrations. Unwittingly, physicians or healthcare workers can be drawn into the situation attempting to help the child based upon the parent's descriptions of what is occurring. Healthcare professionals might prescribe unnecessary diagnostic tests or treatments for the child (Yates & Bass, 2017). Healthcare professionals need increased awareness of MSBP and should question cases where children are seen constantly for parental reported conditions not witnessed by anyone else or if siblings of the child have had similar hospitalizations or have died from SIDS or under suspicious circumstances. Cases where children who are not gaining weight begin to gain during hospitalization are also suspect. If the parent is approached and refuses to get psychological help, or if the child has been subjected to a major illness because of the parent, then the child may need to be placed into a protective environment. MSBP has long-term psychological implications for the child, including PTSD, behavioral problems, and depression (Yates & Bass, 2017).

PERINATAL CARE IN DEVELOPING NATIONS

Pregnant women in developing nations have many of the same risk factors for prematurity and LBW as women in the United States. Such as poor prepregnancy physical condition, inadequate spacing between pregnancies, inadequate nutrition, decreased weight gain during pregnancy, maternal anemia, and lack of access for perinatal care. They also have to contend with other risk factors not even seen in the United States such as diseases like malaria and lack of sanitation. Availability of safe clean water is becoming a global

problem. Poverty and lack of education about pregnancy health are sometimes compounded by lack of skilled care providers, lack of transportation to healthcare centers, problems of war, civil unrest, and low status of women (WHO, 2016b).

Decreasing worldwide maternal and neonatal mortality rates is a priority of the United Nations SDGs. Maternal mortality rates have declined 44% between 1990 and 2015 in response to global efforts toward achieving the Millennial Development Goals. Partnership programs have developed in many countries to improve access to birth control and prenatal care. Management of chronic diseases such as HIV and malaria, efforts to assure a skilled attendant at delivery, and use of evidence-based practices are beginning to make a positive difference (UNICEF, 2018). However, the numbers of maternal deaths are still too high; approximately 303,000 mothers died worldwide due to complications of pregnancy and childbirth in 2015. Almost 99% of these deaths occurred in developing countries, with the highest rates in Africa and South Asia (WHO, 2018c).

Globally, the neonatal mortality rate declined more slowly and fell from 37 per 1,000 births in 1990 to 19 per 1,000 births in 2016 (Hug et al., 2017). Neonatal mortality fell by 49% between 1990 and 2016 but still accounts for more than 46% of deaths in children younger than age 5 worldwide, representing an increase. The worldwide average is 19 neonatal deaths per 1,000 live births, ranging from 3 neonatal deaths per 1,000 live births for high-income countries to 27 neonatal deaths per 1,000 live births in low-income countries. Stillbirth rates globally average 19 stillbirths per 1,000 live births, with a range from 3 per 1,000 live births in high-income countries to 29 per 1,000 in low-income countries prior to 2014 (WHO, 2014). Improved prenatal care, having a skilled attendant at delivery, improved use of hygienic practices for clamping and care of the umbilical cord, and concerted efforts to provide basic resuscitation equipment and training in neonatal resuscitation have had good results in some countries, but much work still needs to be done (WHO, 2014).

Many neonates worldwide have died from preventable conditions. Some congenital anomalies could have been prevented with maternal folic acid supplementation. Many newborns die from birth asphyxia, which might have been prevented through use of timely neonatal resuscitation at delivery. Some deaths from prematurity might have been prevented with adequate prenatal care or a system of basic neonatal care for premature infants. Some deaths from infections could have been prevented with use of hygienic practices at birth, patient teaching about cord care, immunizations, maternal screening for communicable disease risks, or treatment for HIV during pregnancy. Keys to making changes include creating funding partnerships, improving infrastructure, professional education, and implementation of culturally appropriate evidence-based care.

Interventions to improve birth outcomes and decrease neonatal loss in developing nations have been instituted through efforts of WHO, UNICEF, USAIDS, and organizations of UN member nations. These perinatal programs can be tailored to meet the specific needs of each country. As stated by Ban Ki-Moon, United Nations Secretary General:

> To meet the Every Woman Every Child Vision and the Global Strategy for Women's, Children's, and Adolescent's health, we need innovative, evidence-based approaches to antenatal care. I welcome these guidelines, which aim to put women at the centre of care, enhancing their experience of pregnancy and ensuring that babies have the best possible start in life. (WHO, 2016a, p. iv)

Antenatal care is implemented on a local level not only for screening for possible problems but also to educate women about how to promote a healthy pregnancy. Optimal timing and spacing of pregnancy is another important part of prenatal care to promote mothers who are in the best physical condition prior to conception. Prevention and control of infection are also important during the prenatal period. Proper medical treatment of women who are infected with STIs or HIV/AIDS during pregnancy will increase the infant's chances of healthy survival.

Antenatal screening alone can't predict or prevent most problems during pregnancy or delivery; therefore, all pregnant women should be considered high risk and must have access to skilled birth attendants and timely emergency obstetric care. Nations with the highest rates of neonatal and maternal mortality are those that have the lowest number of births attended by a skilled birth attendant. In some countries, access to medical care is difficult due to living in remote village locations, a lack of basic transportation, or poor infrastructure, making it difficult to transport women or infants with problems to specialized centers. Sometimes the policies of developing nations interfere with the provision of safe obstetric care. The current WHO (2018d) recommendations for antenatal care stress the differences for expected care with diverse populations.

Basic training and equipment for infant resuscitation at birth will help prevent some of the poor birth outcomes related to birth asphyxia. Many facilities in developing nations are working with antiquated equipment as they attempt to provide care for neonates. Textbooks are often outdated or are not written in the native language of the healthcare provider. The AAP Neonatal Resuscitation Program (NRP) has been demonstrated to be an effective method to provide immediate resuscitative care to neonates. This program has been translated into at least 24 languages and has been taught in over 130 countries through formally organized courses through the AAP or by independent efforts of NRP instructors (AAP, n.d.). The Helping Babies Survive program is a suite of evidence-based infant resuscitation programs designed for settings where human or technology resources are limited. It is not designed to replace NRP but serves as an adjunct for training birth attendants in how to assess and stimulate breathing during the initial Golden Minute of life. Neonatal mortality is lower when the mother has received professional care during the antenatal period and during childbirth.

Postpartum care that includes parent teaching about infant care and family planning services to help prevent close intrapregnancy levels is included in the UN strategies addressing women's and children's health (UN, 2016). Strategies for successful breastfeeding, proper cord care, recognition of signs of illness, and promotion of psychosocial well-being are all skills that parents need to have in order to promote optimal newborn health. Women of childbearing age need to learn the importance of being in optimal physical condition prior to and during pregnancy. Family planning services will help women become empowered to make choices about when to have children and will help prevent unnecessary abortions.

SUMMARY

This chapter has presented an overview of some of the many prenatal, intrapartum, and postpartum risk factors that influence neonatal health, especially in relation to prematurity and LBW. The perinatal nurse must be aware of potential risk factors in order to screen pregnant women and provide counseling and support. The presence of risk factors can raise suspicion that a baby might have problems after delivery; however, many more babies, even in the presence of multiple risk factors, will be born healthy. Anticipation

of neonates at risk helps assure that adequate personnel and equipment are available at birth to manage problems should they occur. Patient education about modifiable risk factors and support for altering detrimental healthcare behaviors can help prevent some adverse neonatal outcomes.

Some inroads have been made to improve maternal and child health internationally. There are still many barriers for many nations, including creation of the infrastructure needed to support the WHO United Nations goals set forth in the SDG (UN, 2015). Recommendations and training of adequate healthcare professionals to provide care will take commitment and monetary resources of multiple nations. Some countries are beginning to see successes in reducing their maternal and infant mortality. A sustained worldwide effort is needed to continue to improve these outcomes.

CASE STUDY

Identification of the Problem. A 29-year-old woman arrives at the clinic reporting she had a positive home pregnancy test in the past week. Her last menstrual period (LMP) was 4 months ago. The nurse practitioner assesses the woman for potential antepartum risk factors during the first prenatal visit.

Assessment, History

- *Menstrual history:* Menarche at age 12. Reports her periods are regular every 30 days with duration of 4 to 5 days. LMP was 4 months ago on March 10.
- *Obstetric history:* G4T3P0A0L3—reports she had three previous pregnancies. The first pregnancy was a term vaginal delivery 12 years ago. The female infant weighed 3,570 g at birth and is in good health today. The second vaginal delivery 6 years later was a term male born at 40w 4d gestation weighing 3,830 g. He is now 5 years old and in good health. The third vaginal delivery was a term male infant at 40w 2d gestation and weighed 3,800 g. The child is now 3 years old and reported to be in good health. Estimated date of confinement is December 17.
- *Past gynecologic history:* Reports she uses no contraception because she does not believe in taking birth control pills. Reports having a history of multiple sexual partners, currently in monogamous relationship. Was treated for unspecified sexually transmitted infection (STI) 2 years ago at a state health department clinic. HIV status is negative. Reports blood type is O+.
- *Past medical history:* Reports she had acute idiopathic pancreatitis as a teenager but avoided any symptoms or "flare-ups" during her previous pregnancies by watching her diet. Reports she had mild hypertension in the last trimester of last pregnancy that was managed with decreasing her work hours.
- *Drug/substance abuse history:* Denies taking any prescription, over-the-counter, homeopathic, or street drugs. Has not taken prenatal vitamins. Smokes 10 to 12 cigarettes a day. Alcohol: consumes two to three beers a week. Denies alcohol use since she found out she was pregnant.
- *Family/social history:* Lives with husband who is father of baby. Denies familial history of genetic problems. Employed part-time as waitstaff in a casual dining restaurant. Reports husband yells at her a lot and gets angry easily. Reports they are getting along great now.

Physical Examination

- *Neurological:* alert, oriented; pupils dilated, equal and reactive to light and accommodation; DTRs 2+ bilaterally without clonus
- *Head and neck:* neck supple, thyroid examination unremarkable; denies headache, blurred vision, flashing lights in eyes, or scotoma
- *Cardiovascular:* heart rate regular without murmur; denies palpitations, chest pain
- *Respiratory:* lungs clear to auscultation; denies history of asthma, TB, or bronchitis; reports chronic smoker's cough; denies thick sputum
- *Abdomen/Gastrointestinal:* gravid abdomen, distended, fundal height 20 cm, uterine fundus at umbilicus; bowel sounds present, active; denies problems with constipation or diarrhea; reports appetite is fair, occasional nausea and vomiting
- *Genitourinary:* denies vaginal spotting or cramping; reports urinary frequency during the day; denies burning with urination
- *Extremities:* No edema noted in pretibial area. DTRs 2+
- *Other:* reports backache when standing for prolonged periods at work; reports breast tenderness, no colostrum noted

Diagnostic Tests

- Blood type: O+
- Hgb: 10.9; Hct: 34%
- HIV test: negative
- Vaginal cultures: negative
- 50 g 1 hour oral glucose test results: 130 mg/dL
- 100 g 3 hour glucose tolerance test (GTT) results:
  - Fasting: 130 mg/dL
  - 1 hour: 190 mg/dL
  - 2 hour: 155 mg/dL
  - 3 hour: 138 mg/dL

Working Nursing Diagnoses

- Increased risk for prematurity due to history of smoking.
- Increased risk for gestational diabetes due to previous pregnancy and medical history
- Increased risk for PIH due to previous history
- Increased risk for infection related to history of STIs
- Increased risk for injury due to anemia
- Increased risk for injury related to potential physical abuse from significant other
- Increased risk to fetus for FAS due to report of maternal drinking
- Increased risk for SGA infant due to maternal smoking
- Increased risk for LGA infant due to previous history

Development of Management Plan

1. Counsel regarding alcohol use in pregnancy, consider outpatient treatment
2. Provide contact information for emergency women's shelter
3. Teach danger signs during pregnancy and symptoms of PTL and when to notify practitioner
4. Encourage smoking cessation and provide resources

5. HIV testing, screen/treat for STIs
6. Obtain GTT at 24 weeks, follow blood glucose closely
7. Dietary counseling for iron, diabetic diet, limiting fats
8. Promote breastfeeding
9. Serial ultrasounds to monitor infant growth

■ **Implementation.** The patient and nurse discussed needed lifestyle modifications during pregnancy and developed a plan to support the patient counsel; refer to support group for smoking cessation. Mother agreed to attend smoking cessation group for pregnant women. Patient agreed to refrain from alcohol usage during pregnancy. HIV testing completed. Completed GTT at 28 weeks and was referred for nutritional counseling for GDM and sources of iron in diet. Daily iron supplementation provided. Fetal growth was monitored with serial ultrasounds. Patient instructed in how to monitor daily fetal kick counts at 34 weeks.

■ **Evaluation of Effectiveness.** Patient attended smoking cessation group and reported that she cut down her smoking while pregnant to two to three cigarettes a day. She also reported she refrained from use of alcohol during remainder of pregnancy and avoided second-hand smoke outside at the workplace. GTT was positive for GDM, but she was able to maintain control of blood glucose with diet and exercise. She also developed mild hypertension and 3+ proteinuria during the last weeks of pregnancy that was managed with bed rest in the last 2 weeks of pregnancy.

■ **Outcome.** Patient had labor induced at 38 weeks' gestation and delivered a 3,860-g girl. Her Apgar scores at 1 and 5 minutes were 8 and 9. Infant had no hypoglycemia after birth. No signs of FAS noted on admission physical examination. The mother decided to use an intrauterine device (IUD) for birth control following this delivery. Mother was discharged breastfeeding the infant and scheduled for follow-up postpartum visit and IUD insertion in 6 weeks.

EVIDENCE-BASED PRACTICE BOX

Adoption of the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria has resulted in increasing the identification of gestational diabetes (Trujillo et al., 2015). Worldwide prevalence of gestational diabetes mellitus (GDM) is difficult to establish. Currently, research is being undertaken utilizing the IADPSG and WHO (2013) criteria to better assess and intervene with diverse populations (Hagiwara et al., 2018; Tan et al., 2017; Wong et al., 2017). In the United States, there are ethnic variations in prevalence of GDM, with Asian, Hispanic, and Native American women having higher rates than NHB and NHW women. Identification and treatment of women with gestational diabetes is the key to promoting positive neonatal outcomes.

Currently, pregnant women in the United States are screened for gestational diabetes following review of patient history, presence of clinical risk factors, and administration of a 50-g 1-hour oral glucose tolerance test (OGTT). If positive, a second step 100-g 3-hour OGTT follows. The ADA recommends a 75-g OGTT at 24 to 28 weeks with blood glucose measurement when fasting, and at 1 and 2 hours after blood glucose administration. The diagnosis of gestational diabetes is based upon results of the blood glucose screening which exceed predetermined laboratory values for the test.

Adverse outcomes for mother and infant when affected by GDM include risk for cesarean delivery, birth trauma or injuries, and hypoglycemia. Large for gestational age (LGA) is defined as greater than 90th percentile for weight adjusted for gender and gestational weeks at delivery. Prenatal care which includes maternal assessment for GDM and continued fetal surveillance for fetal size may improve outcomes.

Review of Studies

Diagnostic Recommendations and Criteria

The IADPSG, a collaboration formed in 1998, suggested revision of the methods and timing of prenatal screening for gestational diabetes in women. Kong, Lim, and Thompson (2015) conducted a retrospective analysis of patient records comparing the rate of diagnosis of GDM and maternal/fetal outcomes after implementation of IADPSG methods and criteria versus the Carpenter & Coustan (C&C) used previously. IADPSG recommendations include a fasting blood glucose and glycated hemoglobin (A1C) at the first prenatal appointment for those identified at risk for GDM. A second 75-g OGTT is administered at 24 to 28 weeks' gestation to women who did not previously test positive for possible overt diabetes (IADPSG Consensus Panel, 2010). After analysis, Kong et al. (2015) found that use of the IADPSG recommendations resulted in increased diagnosis of GDM but there was no significant maternal/fetal outcomes in either cohort.

Appropriateness of Recommendations Internationally

WHO currently suggests individual countries decide on the methods and criteria for diagnosing diabetes in pregnant women or GDM (WHO, 2016a). If a woman is considered at risk, a fasting specimen is taken at the first prenatal visit. This is followed by a 75-g OGTT between 24 and 28 weeks' gestation. Hagiwara et al. (2018) performed a retrospective review of records to determine if there was a difference in adverse outcomes in Japanese women diagnosed with early pregnancy versus those with mid-pregnancy diagnosis using the international criteria. Results of the study did not demonstrate any differences in the early and mid-pregnancy diagnostic groups. The study investigators determined that the IADPSG recommendations and criteria were not appropriate for Japanese women as there appeared to be no significant difference in outcomes.

A prospective study completed by Hosseini, Janghorbani, and Aminorroaya (2018) in Iran also found increased levels of patients diagnosed with GDM using the One-step test (IADPSG) guidelines over those identified using the Two-step test currently recommended by the ACOG. Women diagnosed by either method had similar pregnancy outcomes, which included

(*continued*)

EVIDENCE-BASED PRACTICE BOX (*continued*)

infants with macrosomia, development of gestational hypertension, and delivery by cesarean section.

Gestational Diabetes in the United States and Recommendations

There is a significant prevalence of GDM in the United States (Martin et al., 2018) with the highest rates among women of Asian race. Prepregnancy diabetes is highest among non-Hispanic Black women. The ACOG currently recommends a two-step approach to prenatal testing for diabetes in pregnancy and GDM. Women considered at risk include those with a previous history of GDM, medical indications, and obesity. Ideally, the woman with diabetes should maintain euglycemia for several months prior to pregnancy, as hyperglycemia in early pregnancy has been associated with increased risk for pregnancy loss and serious congenital defects (Waters et al., 2016). Current recommendations in the United States include blood sugar testing (50-g, 1-hour GTT) at the first prenatal visit if a woman has any risk factors for GDM. Testing is also done at 24 to 28 weeks by a 100-g, 3-hour OGTT. Follow-up for patients after diagnosis includes dietary consultation with nutrition assessment, blood sugar testing daily or more frequently if needed, weight assessments, and fetal assessment for size. If glycemic control is not achieved with improved nutrition measures, then insulin or oral hypoglycemic medications should be considered. Metformin, an oral hypoglycemic, has been used in pregnancy with some success, although caution is still recommended with administration in early pregnancy (Nachum et al., 2017; Vanlalhruaii et al., 2018). The ACOG considers metformin an option especially among women who may not have the desire or ability to self-administer insulin (Caughey & Turrentine, 2018). Glycemic control is an important step in preventing maternal and fetal/newborn complications.

Adverse Maternal, Fetal/Newborn Outcomes

Fetal macrosomia, newborn weight over 4,000 or 4,500 g, is a possible outcome of poor glycemic control in pregnancy (Barth & American College of Obstetricians and Gynecologists, 2016). LGA are those infants over the 90th percentile for gestational age. Assessment during pregnancy of fetal size by measurement and/or ultrasound is not always accurate but has been used to estimate fetal size. Predicted LGA is not considered a reason for induction of labor but may occur in practice. Maternal complications from delivering an LGA infant include perineal trauma and hemorrhage. Poor glycemic control increases the risks for birth defects (i.e., cardiovascular, musculoskeletal, and central nervous system anomalies), hypoglycemia, respiratory complications, and shoulder dystocia (Babović, Arandjelović, Plešinac, Kontić-Vučinić, & Radunović, 2018; Barquiel et al., 2016; Khambalia, Algert, Bowen, Collie, & Roberts, 2017; Yamamoto, Kallas-Koeman, Butalia, Lodha, & Donovan, 2017).

References

Babović, I., Arandjelović, M., Plešinac, S., Kontić-Vučinić, O., & Radunović, N. (2018). Maternal glycoregulation in pregnancies complicated by diabetes mellitus in the prediction of fetal echography findings and perinatal outcomes. *The Journal of Obstetrics and Gynaecology, 44*(3), 432–439. doi:10.1111/jog.13537

Barquiel, B., Herranz, L., Hilhman, N., Burgos, M. A., Grande, C., Tukia, K. M., . . . Pallardo, L. F. (2016). HbA1c and gestational weight gain are factors that influence neonatal outcomes in mothers with gestational diabetes. *Journal of Women's Health, 26*(6), 579–585. doi:10.1089/jwh.2015.5432

Barth, W. H.; American College of Obstetricians and Gynecologists. (2016). Practice bulletin 173: Fetal macrosomia. American College of Obstetricians and Gynecologists. *Obstetrics and Gynecology, 128*(5), e195–e209. doi:10.1097/AOG.0000000000001767

Caughey, A., & Turrentine, M. (2018, February). ACOG practice bulletin number 190: Gestational diabetes mellitus. *Obstetrics and Gynecology, 131*(2), e49–e64. doi:10.1097/AOG.0000000000002501

Hagiwara, Y., Kasai, J., Nokaniski, S., Saigusa, Y., Miyagi, E., & Aoki, S. (2018). Should the IADPSG criteria be applied when diagnosing early onset gestational diabetes? *Diabetes Research and Clinical Practice, 140*, 154–161. doi:10.1016/j.diabres.2018.03.048

Hosseini, E., Janghorbani, M., & Aminorroaya, A. (2018). Incidence, risk factors, and pregnancy outcomes of gestational diabetes mellitus using one-step versus two-step diagnostic approaches: A population-based cohort study in Isfahan, Iran. *Diabetes Research and Clinical Practice, 140*, 288–294. doi:10.1016/j.diabres.2018.04.014

International Association of Diabetes and Pregnancy Study Groups Consensus Panel. (2010). International Association of Diabetes and Pregnancy Groups recommendations on diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care, 33*(3), 676–782. doi:10.2337/dc09-1848

Khambalia, A. Z., Algert, C. S., Bowen, J. R., Collie, R. J., & Roberts, C. L. (2017). Long-term outcomes for large for gestational age infants born at term. *Journal of Paediatrics and Child Health, 53*(9), 876–881. doi:10.1111/jpc.13593

Kong, J. M., Lim, K., & Thompson, D. M. (2015). Evaluation of International Association of Diabetes in Pregnancy Study Groups New criteria: Gestational diabetes project. *Canadian Journal of Diabetes, 39*, 128–132. doi:10.1016/j.jcjd.2014.09.007

Martin, J. A., Hamilton, B. E., Osterman, M. J. K., Driscoll, A. K., & Drake, P. (2018). *Births: Final data for 2017* (National Vital Statistics Report, Vol. 67, No. 8). Retrieved from https://www.cdc.gov/nchs/data/nvsr/nvsr67/nvsr67_08-508.pdf

Nachum, Z., Zafran, N., Salim, R., Hissin, N., Hasanein, J., Letova, Y. G. Z., . . . Yefet, E. (2017). Glyburide versus metformin and their combination for the treatment of gestational diabetes mellitus: A randomized controlled study. *Diabetes Care, 40*, 332–337. doi:10.2337/dc16-2307

Tan, H. L. E., Luu, J., Caswell, A., Holliday, E., Attia, J., & Acharya, S. (2017). Impact of new International Association of Diabetes and Pregnancy Study Groups (IADPSG) diagnostic criteria in a regional tertiary hospital in New South Wales, Australia. *Diabetes Research and Clinical Practice, 134*, 191–198. doi:10.1016/j.diabres.2017.09.016

Trujillo, J., Vigo, A., Duncan, B. B., Falavigna, M., Wendland, E. M., Campos, M. A., & Schmidt, M. I. (2015). Impact of the International Association of Diabetes and Pregnancy Research Study Groups criteria for gestational diabetes. *Diabetes Research and Clinical Practice, 108*, 288–295. doi:10.1016/j.diabres.2015.02.007

Vanlalhruaii, Dasgupta, R., Ramachandran, R., Mathews, J. E., Regi., A., Thomas, N., . . . Thomas, N. (2018). How safe is metformin when initiated in early pregnancy? A retrospective 5-year study of pregnant women with gestational diabetes mellitus from

(*continued*)

EVIDENCE-BASED PRACTICE BOX (*continued*)

India. *Diabetes Research and Clinical Practice, 137*, 47–55. doi:10.1016/j.diabres.2018.01.002

Waters, T. P., Dyer, A. R., Scholtens, D. M., Dooley, S. L., Herer, E., Lowe, L. P., . . . Catalano, P. M.; HAPO Cooperative Study Research Group. (2016). Maternal and neonatal morbidity for women who would be added to the diagnosis of GDM using the IADPSG criteria: A secondary analysis of hyperglycemia and adverse pregnancy outcomes study. *Diabetes Care, 39*(12), 2204–2210. doi:10.2337/dc16-1194

Wong, V. W., Lin, A., & Russell, H. (2017). Adopting new World Health Organization diagnostic criteria for gestational diabetes: How the prevalence changes in a high-risk region in Australia. *Diabetes Research and Clinical Practice, 129*, 148–153. doi:10.1016/j.diabres.2018.03.048

World Health Organization. (2013). *Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy*. Retrieved from http://apps.who.int/iris/bitstream/handle/10665/85975/WHO_NMH_MND_13.2_eng.pdf;jsessionid=337969058560FD3DC04F05700027B356?sequence=1

Yamamoto, J., Kallas-Koeman, M. M., Butalia, S., Lodha, A., & Donovan, L. E. (2017). Large-for-gestational-age (LGA) neonate predicts a 2.5-fold increased odds of neonatal hypoglycaemia in women with type 1 diabetes. *Diabetes/Metabolism Research and Reviews, 33*, e2824. doi:10.1002/dmrr.2824

PARENT VOICES

Ali Dunn

After 3.5 years of infertility and multiple rounds of IVF, finding out I was pregnant was a surprise. Finding out I was expecting twins was shocking, even though I was well aware that the incidence of multiples increases with fertility treatments. Having a high-risk pregnancy due to twins can create additional stress and anxiety. Additional monitoring, appointments with specialists, and careful assessment of the risks involved can take a very natural experience and make it quite medical. Personally, my twin pregnancy started and ended with extreme medical intervention. While it was necessary and lifesaving, it also left me feeling disappointed that my pregnancy experience and birth plans were left unrealized.

Keira Sorrells

Because we did fertility treatments and I was being monitored closely, we knew at our 6-week ultrasound that we were expecting multiples. We were told very quickly that triplets had (at the time) an 85% chance of a successful outcome, meaning little or no NICU time. Our goal was 32 to 34 weeks with the understanding being that they may need a little bit of oxygen, a little help learning how to suck, and a little time to grow. There was very little information shared on the possibility of our babies being born far earlier than 32 weeks. When I was admitted with preeclampsia at 25 weeks, I was totally unprepared, terrified, and sure none of my daughters would survive delivery. I had never seen the inside of the NICU nor had I ever laid eyes on a baby that weighed just 1 lb 4 oz and still had her eyes fused shut. The shock of seeing my three girls as three fetuses outside the womb is something I will not soon forget.

ONLINE RESOURCES

American Academy of Pediatrics. (n.d.). Breastfeeding and medication. Retrieved from https://www.aap.org/en-us/Pages/Breastfeeding-and-Medication.aspx

Association of Women's Health Obstetrics and Neonatal Nurses. (2016a, September). *Position statement: Access to health care*. Retrieved from https://www.jognn.org/article/S0884-2175(16)30424-5/pdf

Association of Women's Health Obstetrics and Neonatal Nurses. (2016b, March). *Position statement: Human trafficking*. Retrieved from http://www.jognn.org/article/S0884-2175(16)30149-6/pdf?utm_source=awhonn.org

Association of Women's Health Obstetrics and Neonatal Nurses. (n.d.). The AWHONN Postpartum Hemorrhage Project. Retrieved from https://www.cdc.gov/ncbddd/fasd/facts.html

Centers for Disease Control and Prevention. (n.d.). *Fetal alcohol spectrum disorders (FASDs): Alcohol use in pregnancy*. Retrieved from last menstrual period (LMP)

European Union National Health System European Office. (2019). The EU and health policy. Retrieved from https://ec.europa.eu/health/home_en

United Nations. (2016). *Every woman every child. Global strategy for women's, children's, and adolescent's health (2016-2030)*. Retrieved from http://globalstrategy.everywomaneverychild.org/pdf/EWEC_globalstrategyreport_200915_FINAL_WEB.pdf

United Nations Children's Fund. (2017). *Levels and trends in child mortality report 2017*. Retrieved from https://data.unicef.org/resources/levels-trends-child-mortality/

World Health Organization. (2014). *Global status report on alcohol and health 2014*. Retrieved from http://www.who.int/substance_abuse/publications/global_alcohol_report/en/

REFERENCES

Altindag, D. T., Baek, D., & Mocan, N. (2017). Chinese yellow dust and Korean infant health. *Social Science Medicine, 186*, 78–86. doi:10.1016/j.socscimed.2017.05.031

American Academy of Pediatrics. (n.d.). *Neonatal Resuscitation Program*. Retrieved from https://www.aap.org/en-us/continuing-medical-education/life-support/NRP/Pages/International.aspx

American College of Obstetricians and Gynecologists. (2018). 2018 legislative priorities. Retrieved from https://www.acog.org/Advocacy/ACOG-Legislative-Priorities?IsMobileSet=false

American College of Obstetricians and Gynecologists. (2013). Committee opinion #759: Definition of term pregnancy (reaffirmed 2017). *Obstetrics and Gynecology, 122*(5), 1139–1140. doi:10.1097/01.AOG.0000437385.88715.4a

Amankwaa, L. C., Rocords, K., Kenner, C., Roux, G., Stone, S. E., & Walker, D. S. (2018). American Academy of Nursing on Policy: African-American mothers' persistent excessive maternal death rates. *Nursing Outlook, 66*(2018), 316–318. doi:10.1016/j.outlook.2018.03.006

Anetor, G. O. (2016). Waste dumps in local communities in developing countries and hidden danger to health. *Perspectives in Public Health, 136*(4), 245–251. doi:10.1177/1757913915626192

Aziato, L., Hindin, M. J., Maya, E. T., Manu, A., Amuasi, S. A., Lawerh, R. M., & Ankomah, A. (2016). Adolescents' responses to an unintended pregnancy in Ghana: A qualitative study. *Journal of Pediatric and Adolescent Gynecology, 29*, 653–658. doi:10.1016/j.jpag.2016.06.005

Babović, I., Arandjelović, M., Plešinac, S., Kontić-Vučinić, O., & Radunović, N. (2018). Maternal glycoregulation in pregnancies complicated by diabetes mellitus in the prediction of fetal echography findings and perinatal outcomes. *The Journal of Obstetrics and Gynaecology, 44*(3), 432–439. doi:10.1111/jog.13537

Balsa, A. I., Caffera, M., & Bloomfield, J. (2016). Exposure to particulate matter from the eruption of the Puychue Volcano and birth outcomes in Montevideo, Uruguay. *Environmental Health Perspectives, 124*(11), 1816–1822. doi:10.1289/ehp235

Barquiel, B., Herranz, L., Hilhman, N., Burgos, M. A., Grande, C., Tukia, K. M., . . . Pallardo, L. F. (2016). HbA1c and gestational weight gain are factors that influence neonatal outcomes in mothers with gestational diabetes. *Journal of Women's Health, 26*(6), 579–585. doi:10.1089/jwh.2015.5432

Barth, W. H.; American College of Obstetricians and Gynecologists. (2016). Practice bulletin no. 173: Fetal macrosomia. *Obstetrics and Gynecology, 128*, e195–e209. doi:10.1097/AOG.0000000000001767

Berhman, R. E., & Butler, A. S. (Eds.). (2007). *Preterm birth: Causes, consequences, and prevention*. Washington, DC: National Academies Press.

Berger, K. E., Masterson, J., Mascardo, J., Grayson, J., Appanaitis, I., Temengil, E., . . . Cash, H. (2016). The effects of chewing betel nut with tobacco and pre-pregnancy obesity on adverse birth outcomes among Palauan women. *Maternal and Child Health Journal, 20*, 1696–1703. doi:10.1007/s10995-016-1972-6

Bhandari, N. R., Day, K. D., Payakachat, N., Franks, A. M., McCain, K. R., & Ragland, D. (2018). Use and risk perception of electronic nicotine delivery systems and tobacco in pregnancy. *Women's Health Issues, 28*(3), 251–257. doi:10.1016/j.whi.2018.02.005

Bhatt, C. B., & Beck-Sagué, C. M. (2018). Medicaid expansion and infant mortality in the United States. *American Journal of Public Health, 108*, 565–567. doi:10.2105/AJPH.2017.304218

Bhuiya, N., House, L. D., Desmarais, J., Fletcher, E., Conlin, M., Perez-McAdoo, S., . . . Tendulkar, S. A. (2017). Strategies to build readiness in community mobilization efforts for implementation in a multi-year teen pregnancy prevention initiative. *Journal of Adolescent Health, 60*, s51–s56. doi:10.1016/j.jadohealth.2016.11.001

Brosens, I., Muter, J., Gargett, C. E., Puttemans, P., Benagiano, G., & Brosens, J. J. (2017). The impact of uterine immaturity on obstetrical syndromes during adolescence. *American Journal of Obstetrics and Gynecology, 217*(5), 546–555. doi:10.1016/j.ajog.2017.05.059

Broughton, D. E., & Moley, K. H. (2017). Obesity and female infertility: Potential mediators of obesity's impact. *Fertility and Sterility, 107*(4), 840–847. doi:10.1016/j.fertnstert.2017.01.017

Burton, G. J., & Jauniaux, E. (2018). Pathophysiology of placental derived fetal growth restriction. *American Journal of Obstetrics and Gynecology, 218*(2), S803–S817. doi:10.1016/j.ajog.2017.11.577

Butler, A. J., Rehm, J., & Fisher, B. (2017). Health outcomes associated with crack-cocaine: Systemic review and meta-analysis. *Drug and Alcohol Dependence, 180*, 401–416. doi:10.1016/j.drugalcdep.2017.08.036

Butterfield, N., Schultz, T., Rasmussen, P., & Proeve, M. (2017). Yoga and mindfulness for anxiety and depression and the role of mental health professionals: A literature review. *The Journal of Mental Health Training, Education and Practice, 12*(1), 44–54. doi:10.1108/JMHTEP-01-2016-0002

Carreau, A.-M., Nadeau, M., Marceau, S., Marceau, P., & Weisnagel, S. J. (2017). Pregnancy after bariatric surgery: Balancing risks and benefits. *Canadian Journal of Diabetes, 41*, 432–438. doi:10.1016/j.jcjd.2016.09.005

Carter, R. C., Jacobson, J. L., Molteno, C. D., Dodge, N. C., Meintjes, E. M., & Jacobson, S. W. (2016). Fetal alcohol growth restriction and cognitive impairment. *Pediatrics, 138*(2), e20160775. doi:10.1542/peds.2016-0775

Centers for Disease Control and Prevention. (n.d.-a). *Assisted reproductive technology. 2015 Assisted Reproductive Technology National Summary Report figures*. Retrieved from https://www.cdc.gov/art/reports/2015/national-summary-figures.html

Centers for Disease Control and Prevention. (n.d.-b). *Assisted reproductive technology (ART)*. Retrieved from https://www.cdc.gov/art/artdata/index.html

Centers for Disease Control and Prevention. (n.d.-c). *Listeria (Listeriosis): People at risk—Pregnant women and newborns*. Retrieved from https://www.cdc.gov/listeria/risk-groups/pregnant-women.html

Centers for Disease Control and Prevention. (n.d.-d). *Sudden unexpected infant death and sudden infant death syndrome: Data and statistics*. Retrieved from https://www.cdc.gov/sids/data.htm

Central Intelligence Agency. (n.d.). *The world factbook*. Retrieved from https://www.cia.gov/library/publications/the-world-factbook/

Chabarria, K. C., Racusin, D. A., Antony, K. M., Kahr, M., Suter, M. A., Mastrobattista, J. M., & Aagaard, K. M. (2016). Marijuana use and its effects in pregnancy. *American Journal of Obstetrics and Gynecology, 215*, 506.e1–506.e7. doi:10.1016/j.ajog.2016.05.044

Chang, Y., Kim, J., & Chatterjee, S. (2017). The association between consumer competency and *Supplemental Nutrition Assistance Program* participation on food insecurity. *Journal of Nutrition Education and Behavior, 49*, 657–666. doi:10.1016/j.jneb.2017.01.008

Chauhan, S. P., Rice, M. M., Grobman, W. A., Bailit, J., Reddy, U. M., Wapner, R. J., . . . Tolosa, J. E. (2017, September). Neonatal morbidity of small- and large-for-gestational age neonates born at term in uncomplicated pregnancies. *Obstetrics and Gynecology, 130*(3), 522–519. doi:10.1097/AOG.0000000000002199

Chevallier, M., Debillion, T., Pierrat, V., Deloeme, P., Kayem, G, Durox, M., . . . Bodeau-Livinec, F. (2017). Leading causes of preterm delivery as a risk factor for intraventricular haemorrhage in very premature infants: Results of the EPIPAGE2 cohort study. *American Journal of Obstetrics and Gynecology, 216*, 518.e1–518.e12. doi:10.1016/j.ajog.2017.01.002

Chevrot, A., Kayem, G., Coupayne, M., Lesage, N., Msika, S., & Mandelbrot, L. (2016). Impact of bariatric surgery on fetal growth restriction: Experiences of a perinatal and bariatric surgery center. *American Journal of Obstetrics and Gynecology, 214*, 655.e1–655.e7. doi:10.1016/j.ajog.2015.11.017

Christian, C. W.; AAP Committee on Child Abuse and Neglect & AAP Section on Child Abuse and Neglect. (2015). *Understanding abusive head trauma in infants and children*. Itasca, IL: American Academy of Pediatrics. Retrieved from https://www.aap.org/en-us/Documents/cocan_understanding_aht_in_infants_children.pdf

Cohen, A., Osorio, R., & Page, L. M. (2017). Substance misuse in pregnancy. *Obstetrics, Gynaecology, and Reproductive Medicine, 27*(10), 316–321. doi:10.1016/j.ogrm.2017.07.003

Collins, J. W., Rankin, K. M., & David, R. J. (2016). Paternal lifelong socioeconomic position and low birth weight rates: Relevance to the African-American women's birth outcome disadvantage. *Maternal and Child Nursing Journal,* 20, 1759–1766. doi:10.1007/s10995-016-1981-5

Cox, S. N., Guidera, K. E., Simon, M. J., Aletta, B., Nonyane, S., Briegeo, W., . . . Kruger, P. S. (2018). Interactive malaria education intervention and its effect on community participant knowledge: The malaria awareness program in Vhembe District, Limpopo, South Africa. *International Quarterly of Community Health Education, 38*(2), 147–158. doi:10.1177/0272684X17749573

Craft-Blacksheare, M. G. (2017). Lessons learned from the crisis in Flint, Michigan regarding the effects of contaminated water on maternal and child health. *Journal of Obstetric, Gynecologic, and Neonatal Nursing, 46*, 258–266. doi:10.1016/j.jogn.2016.10.012

Cross-Barnet, C., Courtot, B., Hill, I., Benatar, S., Checks, M., & Markell, J. (2018). Facilitators and barriers to healthy pregnancy spacing among Medicaid beneficiaries: Findings from the National Strong Start Initiative. *Women's Health Issues, 28*(2), 152–157. doi:10.1016/j.whi.2017.12.004

Dahlin, S., Gunnerbeck, A., Wikström, A.-K., Cnattingius, S., & Edstedt Bonamy, A.-K. (2016). Maternal tobacco use and extremely premature birth-a population-based cohort study. *British Journal of Obstetrics and Gynecology, 123*, 1938–1946. doi:10.1111/1471-0528.14213

Damron, K. R. (2017). Review of the relationships among psychological stress, second hand smoke, and perinatal smoking. *Journal of Obstetric, Gynecologic, and Neonatal Nursing, 46*, 325–333. doi:10.1016/j.jogn.2017.01.012

Dashe, J. S. (2016). Aneuploidy screening in pregnancy. *Obstetrics and Gynecology, 128*(1), 181–194. doi:10.1097/AOG.0000000000001385

De Carvalho, N. S., De Carvalho, B. F., Fugaça, C. A., Dóris, B., & Biscaia, E. S. (2016). Zika virus infection during pregnancy and microcephaly occurrence: A review of literature and Brazilian data. *The Brazilian Journal of Infectious Diseases, 20*(3), 282–289. doi:10.1016/j.bjid.2016.02.006

Dekker, R. L. (2016). Labour induction for late-term or post-term pregnancy. *Women and Birth, 29*, 394–398. doi:10.1016/j.wombi.2016.01.007

Downes, K. L., Shenassa, E. D., & Grantz, K. L. (2017). Neonatal outcomes associated with placental abruption. *American Journal of Epidemiology, 186*(12), 1319–1328. doi:10.1093/aje/kwx202

Dubowitz, L. M., Dubowitz, V., & Goldberg, C. (1970). Clinical assessment of gestational age in the newborn infant. *Journal of Pediatrics, 77*(1), 1–10. doi:10.1016/S0022-3476(70)80038-5

Dufer, H., & Godfrey, K. (2017). Integration of safe sleep and sudden infant death syndrome (SIDS) education among parents of preterm infants in the Neonatal Intensive Care Unit (NICU). *Journal of Neonatal Nursing, 23*, 103–108. doi:10.1016/j.jnn.2016.09.001

Dumas, S. A., Terrell, I. W., & Gustafson, M. (2018). Health and social needs of young mothers. *American Journal of Maternal/Child Nursing, 43*(3), 146–152. doi:10.1097/NMC.0000000000000427

Ehsanipoor, R. (2018). ACOG practice bulletin no. 188 summary. Prelabor rupture of membranes. *Obstetrics and Gynecology, 131*(1), 187–189. doi:10.1097/AOG.0000000000002449

Eke, A. C., Saccone, G., & Berghella, V. (2016). Selective serotonin reuptake inhibitor (SSRI) use during pregnancy and risk of preterm birth: A systematic review and analysis. *British Journal of Obstetrics and Gynaecology, 123*, 1900–1907. doi:10.1111/1471-0528.14144

Epler, K. E., Pierce, A., & Rappaport, V. J. (2017). Pica in pregnancy: An unusual presentation. *Obstetrics and Gynecology, 130*(6), 1377–1379. doi:10.1097/AOG.0000000000002365

Eppes, C., Rac, M., Dunn, J., Versalovic, J., Murray, K. O., Suter, M., . . . Aagaard, K. M. (2017). Testing for Zika virus infection in pregnancy: Key concepts to deal with an emerging epidemic. *American Journal of Obstetrics and Gynecology, 216*(3), 209–225. doi:10.1016/j.ajog.2017.01.020

Eugene, I., & Abedinego, A. (2017). Grandmultiparity: Is it really an independent predictor of adverse pregnancy outcomes? *Saudi Journal for Health Science, 6*, 77–82. doi:10.4103/sjhs.sjhs_98_16

Felder, J. N., Baer, R. J., Rand, L., Jelliffe-Pawlowski, L. L., & Prather, A. A. (2017). Sleep disorder diagnosis during pregnancy and risk of preterm birth. *Obstetrics and Gynecology, 130*(3), 573–581. doi:10.1097/AOG.0000000000002132

Figueras, F., Caradeux, J., Crispi, F., Eixarch, E., Peguero, A., & Gratacos, E. (2018). Diagnosis and surveillance of late-onset fetal growth restriction. *American Journal of Obstetrics and Gynecology, 218*, S790–S802.e1. doi:10.1016/j.ajog.2017.12.003

Fitzgerald, B., Boyle, C., & Honein, M. A. (2018). Birth defects potentially related to Zika virus during pregnancy in the United States. *Journal of the American Medical Association, 319*(12), 1195–1196. doi:10.1001/jama.2018.0126

Fitzpatrick, K. E., Tuffnell, D., Kurinczuk, J. J., & Knight, M. (2016). Pregnancy and very advanced maternal age: A UK population-based cohort study. *British Journal of Obstetrics and Gynaecology, 124*, 1097–1106. doi:10.1111/1471-0528.14269

Folk, D. M. (2018). Hypertensive disorders of pregnancy: An overview and current recommendations. *Journal of Midwifery and Women's Health, 63*, 289–300. doi:10.1111.jmwh.12725

Frederiksen, L. E., Ernst, A., Brix, N., Braskhøj Lauridsen, L. L., Roos, L., Ramlau-Hansen, C. H., & Ekelund, C. K. (2018). Risk of adverse pregnancy outcomes at advanced maternal age. *Obstetrics and Gynecology, 131*(3), 457–463. doi:10.1097/AOG.0000000000002504

Galloway, C. T., Duffy, C. T., Dixon, R. P., & Fuller, T. R. (2017). Exploring African-American and Latino teens' perceptions of contraception and access to reproductive health care services. *Journal of Adolescent Health, 60*, s57–s62. doi:10.1016/j.jadohealth.2016.12.006

Garland, M. (2017). Physical activity during pregnancy: A prescription for improved perinatal outcomes. *The Journal for Nurse Practitioners, 13*(1), 54–58. doi:10.1016/j.nurpra.2016.07.005

Gehlawat, P., Gehlawat, V. K., Singh, P., & Gupta, R. (2015). Munchausen syndrome by proxy: An alarming face of child abuse. *Indian Journal of Psychological Medicine, 37*(1), 90–92. doi:10.4103/0253-7176.150850

Geller, P. A., & Stasko, E. C. (2017). Effect of previous posttraumatic stress in the perinatal period. *Journal of Obstetric, Gynecologic and Neonatal Nursing, 46*, 912–922. doi:10.1016/j.jogn.2017.04.136

Gonzales, S., & Sawyer, B. (2017). *How does infant mortality in the U.S. compare to other countries?* Retrieved from https://www.healthsystemtracker.org/chart-collection/infant-mortality-u-s-compare-countries/#item-neonatal-mortality-u-s-higher-comparable-countries

Gordijn, S. J., Beune, I. M., & Ganzevoort, W. (2018). Building consensus and standards in fetal growth restriction studies. *Best Practices and Research Clinical Obstetrics and Gynaecology, 49*, 117–126. doi:10.1016/j.bpobgyn.2018.02.002

Gunier, R. B., Bradman, A., Harley, K. G., Kogut, K., & Eskenazi, B. (2017). Prenatal residential proximity to agricultural pesticide use and IQ in 7-year-old children. *Environmental Health Perspectives, 125*(5), 057002. doi:10.1289/EHP504

Haas, D. M., Marsh, D. J., Dang, D. T., Parker, C. B., Wing, D. A., Simhan, H. N., . . . Reddy, U. M. (2018). Prescription and other medication use in pregnancy. *Obstetrics and Gynecology, 131*(5), 789–798. doi:10.1097/AOG.0000000000002579

Hagiwara, Y., Kasai, J., Nokaniski, S., Saigusa, Y., Miyagi, E., & Aoki, S. (2018). Should the IADPSG criteria be applied when diagnosing early onset gestational diabetes? *Diabetes Research and Clinical Practice, 140*, 154–161. doi:10.1016/j.diabres.2018.03.048

Hanna-Attisha, M., LaChance, J., Sadler, R. C., & Schnepp, A. C. (2016). Elevated blood lead levels in children associated with Flint drinking water crisis: A spatial analysis of risk and public health response. *American Journal of Public Health, 106*(2), 283–290. doi:10.2105/AJPH.2015.303003

Harrison, W. N., Wasserman, J. R., & Goodman, D. C. (2018). Regional variation in neonatal intensive care admissions and the relationship

to bed supply. *The Journal of Pediatrics, 192*, 73–79. doi:10.1016/j.jpeds.2017.08.028

Heider, A. (2017). Fetal vascular malperfusion. *Archives of Pathology and Laboratory Medicine, 141*, 1484–1489. doi:10.5858/arpa.2017-0212-RA

Herini, E. S., Gunadi, Triono, A., Mulyadi, A. W. E., Mardin, N., Rusipah, . . . Reef, S. E. (2017). Hospital-based surveillance of congenital rubella syndrome in Indonesia. *European Journal of Pediatrics, 176*, 387–393. doi:10.1007/s00431-017-2853-8

Hirai, A. H., Sappenfield, W. M., Ghandour, R. M., Donahue, S., Lee, V., & Lu, M. C. (2018). The Collaborative Improvement and Innovation Network (CoIIN) to reduce infant mortality: An outcome evaluation from the US South, 2011 to 2014. *American Journal of Public Health, 108*, 815–821. doi:10.2105/AJPH.2018.304371

Ho, G. W. K., Bettencourt, A., & Gross, D. A. (2017). Reporting and identifying child physical abuse: How are we doing? *Research in Nursing and Health, 40*, 519–527. doi:10.1002/nur.21818

Hosseini, E., Janghorbani, M., & Aminorroaya, A. (2018). Incidence, risk factors, and pregnancy outcomes of gestational diabetes mellitus using one-step versus two-step diagnostic approaches: A population-based cohort study in Isfahan, Iran. *Diabetes Research and Clinical Practice, 140*, 288–294. doi:10.1016/j.diabres.2018.04.014

Howe, T.-H., Sheu, C.-F., Hsu, Y.-W., Wang, T.-N., & Wang, L.-W. (2016). Predicting neurodevelopmental outcomes at preschool age for children with very low birth weight. *Research in Developmental Disabilities, 48*, 231–431. doi:10.1016/j.ridd.2015.11.003

Howson, C. P., Kinney, M. V., & Lawn, J. E. (Eds). (2012). *Born too soon: The global action report on preterm birth*. Geneva, Switzerland: World Health Organization. Retrieved from http://www.who.int/pmnch/media/news/2012/201204_borntoosoon-report.pdf

Hoyert, D. L., & Gregory, E. C. W. (2016). *Cause of fetal death: Data from the fetal death report, 2014* . (National Vital Statistics Report, Vol. 65, No. 7). Hyattsville, MD: National Center for Health Statistics.

Hug, L., Sharrow, D., & You, D. (2017). *Levels and trends in child mortality. Report 2018*. New York, NY: United Nations Inter-agency Group for Child Mortality Estimates. Retrieved from http://www.childmortality.org/files_v21/download/IGME%20report%202017%20child%20mortality%20final.pdf

Hughes, K., Sim, S., Roman, A., Michalak, K., Kane, S., & Sheehan, P. (2017). Outcomes and predictive tests from a dedicated specialist clinic for women at high risk of preterm labour: A ten year audit. *Australian New Zealand Journal of Obstetrics and Gynaecology, 57*, 405–411. doi:10.1111/ajo.12610

Hurley, E. G., & DeFranco, E. A. (2017). Influence of paternal age on perinatal outcomes. *American Journal of Obstetrics and Gynecology, 217*(5), 566.e1–566.e6. doi:10.1016/j.ajog.2017.07.034

International Confederation of Midwives. (2017). *Strategy 2017-2020*. Retrieved from https://www.internationalmidwives.org/about-us/icm-strategic-directions.html

Jans, G., Matthys, C., Bogaerts, A., Lannoo, M., Verhaeghe, J., Van der Schueren, B., & Devlieger, R. (2015). Maternal micronutrient deficiencies and related adverse neonatal outcomes after bariatric surgery: A systematic review. *Advanced Nutrition, 6*, 420–429. doi:10.3945/an.114.008086

Janssen, B. G., Saenen, N. D., Roels, H. A., Madhloum, N., Gyselaero, W., Lefebvre, W., . . . Nawrot, T. S. (2017). Fetal thyroid function, birth weight, and in utero exposure to fine particle air pollution: A birth cohort study. *Environmental Health Perspectives, 125*, 699–705. doi:10.1289/EHP508

Karahanoglu, E., Akpinar, F., Demirdag, E., Yerebasmag, N., Ensari, T., Akyol, A., . . . Yalva, S. (2016). Obstetric outcomes of isolated oligohydramnios during early-term, full-term, and late-term periods and determination of optimal timing of delivery. *The Journal of Obstetrics and Gynaecology Research, 42*(9), 1119–1124. doi:10.1111/jog.13024

Karakurt, G., Patel, V., Whiting, K., & Koyutürk, M. (2017). Mining electronic health record data: Domestic violence and adverse health effects. *Journal of Family Violence, 32*, 79–87. doi:10.1007/s10896-016-9872-5

Kawakita, T., Wilson, K., Grantz, K., Landy, H., Huang, C.-C., & Gomez-Lolo, V. (2016). Adverse maternal and neonatal outcomes in adolescent pregnancy. *Journal of Pediatric and Adolescent Gynecology, 29*, 130–136. doi:10.1016/j.jpag.2015.08.006

Kelly, P., Thompson, J. M. D., Koh, J., Ameratunga, S., Jelleyman, T., Percival, T. M., . . . Mitchell, E. A. (2017). Perinatal risk and protective factors for pediatric abusive head trauma: A multicenter case-control study. *The Journal of Pediatrics, 187*, 240–246.e4. doi:10.1016/j.jpeds.2017.04.058

Khambalia, A. Z., Algert, C. S., Bowen, J. R., Collie, R. J., & Roberts, C. L. (2017). Long-term outcomes for large for gestational age infants born at term. *Journal of Paediatrics and Child Health, 53*, 876–881. doi:10.1111/jpc.13593

Kim, S. S., Zhu, Y., Grantz, K. L., Hinkle, S. N., Chen, Z., Wallacw, M. E., . . . Mendola, P. (2016). Obstetric and neonatal risks among obese women without chronic disease. *Obstetrics and Gynecology, 128*, 104–112. doi:10.1097/AOG.0000000000001465

Kingdon, J. C., Audette, M. C., Hobson, S., Windrim, R. C., & Morgen, E. (2018). A placenta clinic approach to the diagnosis and management of fetal growth restriction. *American Journal of Obstetrics and Gynecology, 218*, S803–S817. doi:10.1016/j.ajog.2017.11.575

Kiserud, T., Benachi, A., Hecker, K., Perez, R. G., Carvalho, J., Piaggio, G., & Platt, L. (2018). The World Health Organization fetal growth charts: Concept, findings, interpretation, and application. *American Journal of Obstetrics and Gynecology, 218*, S619–S629. doi:10.1016/j.ajog.2017.12.010

Korten, I., Ramsey, K., & Latzin, P. (2017). Air pollution during pregnancy and lung development in the child. *Paediatric Respiratory Reviews, 21*, 38–46. doi:10.1016/j.prrv.2016.08.008

Kozhimannil, K. B., Graves, A. J., Levy, R., & Patrick, S. W. (2017). Nonmedical use of prescription opioids among pregnant U.S. women. *Women's Health Issues, 27*(3), 308–315. doi:10.1016/j.whi.2017.03.001

Kraft, W. K., Stover, M. W., & Davis, J. M. (2016). Neonatal abstinence syndrome: Pharmacologic strategies for the mother and infant. *Seminars in Perinatology, 40*, 203–212. doi:10.1053/j.semperi.2015.12.007

Kumar, N., Raher, C. A., Ware, C. F., & Phipps, M. G. (2017). Characterizing social determinants of health for adolescent mothers during prenatal and postpartum periods. *Women's Health Issues, 27*(5), 565–572. doi:10.1016/j.whi.2017.03.009

Kuper, S. G., Sievert, R., Biggio, J. R., Tita, A. T., & Harper, L. M. (2017). Maternal and neonatal outcomes in indicated preterm births based on the intended mode of delivery. *Obstetrics and Gynecology, 130*(5), 1143–1151. doi:10.1097/AOG.0000000000002320

Kurti, A. N., Redner, R., Lopez, A. A., Keith, D. R., Villanti, A. C., Stanton, C. A., . . . Higgins, S. T. (2017). Tobacco and nicotine delivery product use in a national sample of pregnant women. *Preventive Medicine, 104*, 50–56. doi:10.1016/j.ypmed.2017.07.030

Lee, A. [Alison], Hsu, H.-H. L., Chiu, Y.-H. M., Bose, S., Rosa, M. J., Kloog, I., . . . Wright, R. J. (2018). Prenatal fine particulate exposure and early childhood asthma: Effect of maternal stress and fetal sex. *Journal of Allergy, Clinical Immunology, 141*(5), 1880–1886. doi:10.1016/j.jaci.2017.07.017

Lee, A. C. C. [Anne], Panchal, P., Folger, L., Whelan, H., Whelan, R., Rosner, B., . . . Lawn, J. E. (2017). Diagnostic accuracy of neonatal assessment for gestational age determination: A systemic review. *Pediatrics, 140*(6), e20171423. doi:10.1542/peds.2017-1423

Lee, C., Deng, L., Ou, C., Yuan, H., Chen, X., & Deng, Q. (2017). Preconceptual and perinatal exposure to traffic related air pollution and eczema in preschool children. *Journal of Dermatological Science, 85*, 85–95. doi:10.1016/j.jdermsci.2016.11.004

Leemaqz, S. Y., Dekker, G. A., McCowan, L. M., Kenny, L. C., Myers, J. E., Simpson, N. A. B., . . .Roberts, C. T. (2016). Maternal marijuana use has independent effects on risk for spontaneous preterm birth but not other common late pregnancy complications. *Reproductive Toxicology, 62*, 77–86. doi:10.1016/j.reprotox.2016.04.021

Li, S., Guo, Y., & Williams, G. (2016). Acute impact of hourly ambient air pollution on preterm birth. *Environmental Health Perspectives, 124*(10), 1623–1629. doi:10.1289/EHP200

Liu, P., Wu, C., Chang, X., Qi, X., Zheng, M., & Zhou, Z. (2016). Adverse association of both prenatal and postnatal exposure to organophosphorous pesticides with infant neurodevelopment in an

agricultural area of Jiangsu Province, China. *Environmental Health Perspectives, 124*(10), 1637–1643. doi:10.1289/EHP196

Loopstra, R. (2018). Rising food bank use in the UK: Sign of a new public health emergency? *Nutrition Bulletin, 43*, 53–60. doi:10.1111/nbu.12306

Lopez-Bushnell, K., Torrez, D., Robertson, J. V., Torrez, C., & Strickler, L. (2017). Shaken baby syndrome: A hospital-based education and prevention program in the intermediate care and the newborn intensive care nurseries. *Journal of Neonatal Nursing, 23*, 142–150. doi:10.1016/j.jnn.2016.09.004

Lorthe, E., Ancel, P.-Y., Torchin, H., Kaminski, M., Langer, B., Subtil, D., . . . Kayem, G. (2017). Impact of latency duration on the prognosis of infants after preterm premature rupture of membranes at 24-32 weeks gestation: A national population-based cohort study. *Journal of Pediatrics, 182*, 47–52. doi:10.1016.j.jpeds.2016.11.074

Louis, J. (2018). Obstructive sleep apnea in pregnancy–what you need: Sleep-disordered breathing has implication for both mother and fetus. *Contemporary OB/GYN, 63*(2), 18–22. Retrieved from https://www.uptodate.com/contents/obstructive-sleep-apnea-in-pregnancy

Luke, B. (2017). Pregnancy and birth outcomes in couples with infertility with and without assisted reproductive technology: With an emphasis on US population-based studies. *American Journal of Obstetrics and Gynecology, 217*, 270–281. doi:10.1016/j.ajog.2017.03.012

Luke, B., Gopal, D., Cabral, H., Stern, J. E., & Diop, H. (2017). Adverse pregnancy, birth, and infant outcomes in twins: Effects of maternal fertility status and infant gender combinations; The Massachusetts Outcome Study of Assisted Reproductive Technology. *American Journal of Obstetrics and Gynecology, 217*, 330.e1–e15. doi:10.1016/j.ajog.2017.04.025

Lynch, M. M., Amoozegaar, J. B., McClure, E. M., Squiers, L. B., Broussard, C. S., Lind, J. N., . . . Biermann, J. (2017). Improving safe use of medications during pregnancy: The roles of patients, physicians, and pharmacists. *Qualitative Health Research, 27*(13), 2071–2080. doi:10.1177/1049732317732027

Malacova, E., Regan, A., Nassar, N., Raynes-Greenow, C., Leonard, H., Srinivasjois, R., . . . Periera, G. (2017). Risk of stillbirth, preterm delivery, and fetal growth restriction following exposure in a previous birth: Systemic review and meta-analysis. *British Journal of Obstetrics and Gynecology, 125*, 183–192. doi:10.1111/1471-0528.14906

March of Dimes. (2016). *March of Dimes Foundation data book for policy makers: Maternal, infant, and child health in the United States 2016*. Retrieved from https://www.marchofdimes.org/materials/March-of-Dimes-2016-Databook.pdf

Margerison-Zilko, C. E., Strutz, K. L., & Holzman, C. (2017). Stressors across the life-course and preterm delivery: Evidence from a pregnancy cohort. *Maternal and Child Health Journal, 21*, 648–658. doi:10.1007/s10995-016-2151-5

Martin, J. A., Hamilton, B. E., Osterman, M. J. K., Driscoll, A. K., & Drake, P. (2018). *Births: Final data for 2017* (National Vital Statistics Report, Vol. 67, No. 8). Retrieved from https://www.cdc.gov/nchs/data/nvsr/nvsr67/nvsr67_08-508.pdf

Martin-Nalda, A., Roca, I., Fontecha, C. G., Fernández-Polo, A., Barber, I., Martinez-Gallo, M., & Soler-Palacin, P. (2016). Chronic recurrent multifocal osteomyelitis and thalidomide in chronic granulomatous disease. *Pediatrics, 138*(2), e20154017. doi:10.1542/peds.2015-4017

McCaffrey, M. (2017). Abortion's impact on prematurity: Closing the knowledge gap. *Issues in Law and Medicine, 32*(1), 43–52. (Reprint from *North Carolina Family Policy Council.*)

McCarthy, J. J., Leamon, M. H., Finnegan, L. P., & Fassbender, C. (2017). Opioid dependence and pregnancy: Minimizing stress on the fetal brain. *American Journal of Obstetrics and Gynecology, 216*(3), 226–231. doi:10.1016/j.ajog.2016.10.003

McHugh, M. J., Kvernland, A., & Palusci, V. J. (2017). An adolescent parent's program to reduce child abuse. *Child Abuse Review,* 26, 184–195. doi:10.1002/CAR.2426

McLennon, A. S., Gyamfi-Bannerman, C., Ananth, C. V., Wright, J. D., Saddiq, Z., D'Alton, M. E., & Friedman, A. M. (2017). The role of maternal age in twin pregnancy outcomes. *American Journal of Obstetrics and Gynecology, 217*, 80.e1–80.e8. doi:10.1016/j.ajog.2017.03.002

McNeill, C., Sisson, W., & Jarrett, A. (2017). Listeriosis: A resurfacing menace. *The Journal for Nurse Practitioners, 13*(10), 647–654. doi:10.1016/j.nurpra.2017.09.014

Mehta-Lee, S., Palma, A., Berstein, P. S., Lounsbury, D., & Schlecht, N. (2017). A preconception nomogram to predict preterm delivery. *Maternal and Child Health Journal,* 21, 118–127. doi:10.1007/s10995-016-2100-3

Metz, T. D., Allshouse, A. A., Hogue, C. J., Goldenberg, R. L., Dudley, D. J., Vamer, M. W., . . . Silver, R. M. (2017). Maternal marijuana use and adverse pregnancy outcomes and neonatal morbidity. *American Journal of Obstetrics and Gynecology, 217*, 478.e1–e8. doi:10.1016/j.ajog.2017.05.050

Micali, N., Stemann Larsen, P., Strandberg-Larson, K., & Nybo Anderson, A.-M. (2016). Size at birth and preterm birth in women with lifetime eating disorders: A prospective population-based study. *British Journal of Obstetrics & Gynecology, 123*, 1301–1310. doi:10.1111/1471-0528.13825

Miller Ferguson, N., Sarnaik, A., Miles, D., Shafi, N., Peters, M., Truemper, E., . . . Kochanek, P. M. (2017). Abusive head trauma and mortality—An analysis from an international comparative effectiveness study of children with traumatic brain injury. *Critical Care Medicine, 45*(8), 1398–1407. doi:10.1097/CCM.0000000000002378

Moaddab, A., Chevenak, F. A., Mccllough, L. B., Sangi-Haghpeyker, H., Shamshirsaz, A. A., Schutt, A., . . . Shamshirsaz, A. A. (2017). Effects of advanced maternal age on maternal and neonatal outcomes in assisted reproductive technology pregnancies. *European Journal of Obstetrics and Gynecology and Reproductive Biology, 216,* 178–183. doi:10.1016/j.ejogrb.2017.07.029

Moon, R. Y. (2016). SIDS and other sleep-related deaths: Evidence base for 2016 updates recommendations for a safe infant sleeping environment. *Pediatrics, 138*(5), e20162940. doi:10.1542/peds.2016-2940

Morean, M. E., DeMartimi, K. S., Foster, D., Patock-Peckham, J., Garrison, K. A., Corlett, P. R., . . . O'Malley, S. S. (2018). The self-report habit index: Assessing habitual marijuana, alcohol, e-cigarette, and cigarette use. *Drug and Alcohol Dependence, 186*, 207–214. doi:10.1016/j.drugalcdep.2018.01.014

Morris, J. M., Totterdell, J., Bin, Y. S., Ford, J. B., & Roberts, C. L. (2018). Contribution of maternal age, medical and obstetric history to maternal and perinatal morbidity/mortality for women aged 35 or older. *Australian New Zealand Obstetrics and Gynaecology, 58*, 91–97. doi:10.1111/ajo.12674

Morrison, K. M., Ramsingh, L., Gunn, E., Streiner, D., Van Lieshout, R., & Boyle, M. (2016). Cardiometabolic health in adults born premature with extremely low birth weight. *Pediatrics, 138*(4), e20160515. doi:10.1542/peds.2016-0515

Mulik, K., & Haynes-Maslow, L. (2017). The affordability of MyPlate: An analysis of SNAP benefits and the actual cost of eating according to the dietary guidelines. *Journal of Nutrition Education and Behavior, 49*, 623–631.e1. doi:10.1016/j.jneb.2017.06.005

Murphy, S. L., Xu, J., Kochanek, M. A., Curtin, S. C., & Arias, E. (2017). *CDC deaths final data* (National Statistics Reports, Vol. 66, No. 6). Retrieved from https://www.cdc.gov/nchs/data/nvsr/nvsr66/nvsr66_06.pdf

Myers, B., Koen, N., Donald, K. A., Nhapi, R. T., Workman, L., Barnett, W. . . . Stein, D. J. (2018). Effect of hazardous alcohol use during pregnancy on growth outcomes at birth: Findings from a South African cohort study. *Alcoholism: Clinical and Experimental Research, 42*(2), 369–377. doi:10.1111/acer.13566

Mzayek, F., Cruickshank, J., Amoah, D., Srinivasan, S., Chen, W., & Berenson, G. (2016). Birth weight was longitudinally associated with cardiometabolic risk markers in mid-adulthood. *Annals of Epidemiology, 26*(9), 643–647. doi:10.1016/j.annepidem.2016.07.013

Nachum, Z., Zafran, N., Salim, R., Hissin, N., Hasanein, J., Letova, Y. G. Z., . . . Yefet, E. (2017). Glyburide versus metformin and their combination for the treatment of gestational diabetes mellitus: A randomized controlled study. *Diabetes Care, 40*, 332–337. doi:10.2337/dc16-2307

National Institutes of Health. (n.d.a). *Lactmed: A toxnet database for Drugs and Lactation Database*. Retrieved from https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm

National Institutes of Health. (n.d.b). *Safe to sleep.* Retrieved from https://www1.nichd.nih.gov/sts/about/SIDS/Pages/fastfacts.aspx

Natureeba, P., Kakuru, A., Muhindo, M., Ochieng, T., Ategeka, J., Koss, C. A., . . . Dorsey, G. (2017). Intermittent preventative treatment with dihydroartemesinin-Piperaquine for the prevention of malaria among HIV-infected pregnant women. *The Journal of Infectious Diseases, 216*, 29–35. doi:10.1093/infdis/jix110

Nicholas, P. K., & Breaky, S. (2017). Climate change, climate justice, and environmental health: Implications for the nursing profession. *Journal of Nursing Scholarship, 49*(6), 606–616. doi:10.1111/jnu.12326

Nist, M. D. (2017). Biological embedding: Evaluation and analysis of an emerging concept for nursing scholarship. *Journal of Advanced Nursing, 73*(2), 349–360. doi:10.1111/jan.13168

Nkansah-Amankra, S. (2018). Pre-pregnancy maternal depression symptoms and low birth weight and preterm birth outcomes: Assessment of adolescent background characteristics and birth outcomes in adulthood. *Midwifery, 58*, 120–129. doi:10.1016/j.midw.2017.12.004

Nörby, U., Forsberg, L., Wide, K., Sjörs, G., Winbladh, B., & Källén, K. (2016). Neonatal morbidity after maternal use of antidepressant drugs during pregnancy. *Pediatrics, 138*(5), e20160181. doi:10.1542/peds.2016-0181

Nypaver, C. F., & Shambley-Ebron, D. (2016). Using community-based participatory research to investigate meaningful prenatal care among African American women. *Journal of Transcultural Nursing, 27*(6), 558–566. doi:10.1177/1043659615587587

Nzelu, D., Dumitrascu-Biris, D., Nicolaides, K. H., & Kametas, N. A. (2018). Chronic hypertension: First trimester blood pressure control and the likelihood of severe hypertension, preeclampsia, and small for gestational age. *American Journal of Obstetrics and Gynecology, 218*, 337.e1–337.e7. doi:10.1016/j.ajog.2017.12.235

Onyeneko, N. G., L'Aronu, N., Chukwu, N., Agbawodikeizu, U. P., Chalupowski, M., & Subramanian, S. (2016). Factors associated with compliance to recommended micronutrients uptake for prevention of anemia during pregnancy in urban, peri-urban, and rural communities in Southeast Nigeria. *Journal of Health, Population, and Nutrition, 35*(1), 35. doi:10.1186/s41043-016-0068-7

Ostfeld, B. M., Schwartz-Soicher, O., Reichman, N. E., Teitler, J. O., & Hegyi, T. (2017). Prematurity and sudden unexpected infant deaths in the United States. *Pediatrics, 140*(1), e20163334. doi:10.1542/peds.2016-3334

Pellowski, J. A., Barnett, W., Kuo, C. C., Koen, N., Zar, H., & Stein, D. J. (2017). Investigating tangible and mental resources as predictors of perceived household food insecurity during pregnancy among women in a South African birth cohort study. *Social Science and Medicine, 187*, 76–84. doi:10.1016/j.socscimed.2017.06.022

Plancoulaine, S., Flori, S., Bat-Pitault, F., Patural, H., Lin, J.-S., & Franco, P. (2017). Sleep trajectories among pregnant women and the impact on outcomes: A population-based cohort study. *Maternal and Child Health Journal, 21*, 1139–1146. doi:10.1007/s10995-016-2212-9

Platt, M. J. (2014). Outcomes in preterm infants. *Public Health, 128*, 399–403. doi:10.1016/j.puhe.2014.03.010

Pocobelli, G., Dublin, S., Enquobahrie, D. A., & Mueller, B. A. (2016). Birth weight and birth weight for gestational age in relation to risk of hospitalization with primary hypertension in children and young adults. *Maternal and Child Health Journal, 20*, 1415–1423. doi:10.1007/s10995-016-1939-7

Prasoona, K. R., Sunitha, T., Srinadh, B., Deepika, M. L. N., Kumari, T. M., & Jyothy, A. (2016). Paternal transmission of MTHFD1 G1958A variant predisposes to neural tube defects in offspring. *Developmental Medicine and Child Neurology, 58*(6), 625–631. doi:10.1111/dmcn.12929

Purisch, S. E., & Gyamfi-Bannerman, C. (2017). Epidemiology of preterm birth. *Seminars in Perinatology, 41*, 387–391. doi:10.1053/j.semperi.2017.07.009

Romero, R., Erez, O., Huttemann, M., Maymon, E., Panaitescu, B., Conde-Agudelo, A., . . . Grossman, L. I. (2017). Metformin, the aspirin of the 21st century: Its role in gestational diabetes mellitus, prevention of preeclampsia and cancer, and the promotion of longevity. *American Journal of Obstetrics and Gynecology, 217*, 282–302. doi:10.116/j.ajog.2017.06.003

Rood, K. M., & Buhimschi, C. S. (2017). Genetics, hormonal influences, and preterm birth. *Seminars in Perinatology, 41*, 401–408. doi:10.1053/j.semperi.2017.07.011

Rosenberg, A., & Meyerle, J. (2017). The use of apremilast to treat psoriasis during deployment. *Military Medicine, 182*, 1328–1631. doi:10.7205/,ILMED-D-17-00047

Rosenberg, M. A., Li, Y., & Seng, J. S. (2017). Allostatic load: A useful concept for advancing nursing research. *Journal of Clinical Nursing, 26*, 5191–5205. doi:10.1111/jocn.13753

Royal College of Nurse Midwives. (n.d.). *Position statements*. Retrieved from https://www.rcm.org.uk/promoting/professional-practice/standards-guidance/

Sagiv, S. K., Harris, M. H., Gunier, R. B., Kogut, K. R., Harley, K. G., Deardorff, J., . . . Eskenazi, B. (2018). Prenatal organophosphate pesticide exposure and traits related to autism spectrum disorder in a population living in proximity to agriculture. *Environmental Health Perspectives, 126*(4), 1–9. doi:10.1289/EHP2580

Sanjeevi, N., Freeland-Graves, J., & Hersh, M. (2018). Food insecurity, diet quality and body mass index of women participating in the Supplemental Nutrition Assistance Program: The role of intrapersonal, home environment, community, and social factors. *Appetite, 125*, 109–117. doi:10.1016/j.appet.2018.01.036

Santibañez, S., Lynch, J., Paye, Y. P., McCalla, H., Gaines, J., Konkel, K., . . . Daniel, K. L. (2017). Engaging community and faith-based organizations in the Zika response, United States, 2016. *Public Health Reports, 132*(4), 436–442. doi:10.1177/0033354917710212

Schieve, L. A., Tian, L. H., Rankin, K., Kogan, M., Yeargin-Allsopp, M., Visser, S., & Rosenberg, D. (2016). Population impact of preterm birth and low birth weight on developmental disabilities in US children. *Annals of Epidemiology, 26*, 267–274. doi:10.1016/j.annepidem.2016.02.012

Scoglio, A. A. J., Rudat, D. A., Garvert, D., Jarmolowski, M., Jackson, C., & Herman, J. L. (2018). Self-compassion and response to trauma: The role of emotional regulation. *Journal of Interpersonal Violence, 33*(13), 2016–2036. doi:10.1177/0886260515622296

Shafiq, Y., Khowaja, A. R., Yousafzai, M. T., Ali, S. A., Zaidi, A., & Saleem, A. F. (2017). Knowledge, attitudes and practices related to tetanus toxoid vaccination in women of childbearing age: A cross-sectional study in peri-urban settlements of Karachi, Pakistan. *Journal of Infectious Prevention, 18*(5), 232–241. doi:10.1177/1757177416689722

Shaw, J. G., Asch, S. M., Katon, J. G., Shaw, K. A., Kimerling, R., Frayne, S. M., & Phibbs, C. S. (2017). Post-traumatic stress disorder and antepartum complications: A novel risk factor for gestational diabetes and preeclampsia. *Paediatric and Perinatal Epidemiology, 31*, 185–194. doi:10.1111/ppe.12349

Sievert, R. A., Kuper, S. G., Jauk, V. C., Parrich, M., Biggio, J. R., & Harper, L. M. (2017). Predictors of vaginal delivery in medically indicated early preterm induction of labor. *American Journal of Obstetrics and Gynecology, 217*, 375.e1–375.e7. doi:10.1016/j.ajog.2017.05.025

Silver, R. M. (2015). Abnormal placentation. Placenta previa, vasa previa, and placenta accreta. *Obstetrics and Gynecology, 126*, 654–668. doi:10.1097/AOG.0000000000001005

Sinclair, M., Lagan, B. M., Dolk, H., & McCullough, J. E. M. (2018). An assessment of pregnant women's knowledge and use of the Internet for medication safety information and purchase. *Journal of Advanced Nursing, 74*, 137–147. doi:10.1111/jan.13387.

Singh, K. P., Miaskowski, C., Dhruva, A. A., Flowers, E., & Kober, K. M. (2018). Mechanisms and measurement of change in gene expression. *Biological Research for Nursing, 20*(4), 369–382. doi:10.1177/1099800418772161

Slemming, W., Bello, B., Saloojee, H., & Richter, L. (2016). Maternal risk exposure during pregnancy and infant birth weight. *Early Human Development, 99*, 31–36. doi:10.1016/j.earlhumdev.2016.03.012

Smid, M. C., Lee, J. H., Grant, J., Miles, G., Stoddard, G., Chapman, D., & Manuck, T. (2017). Maternal race and intergenerational preterm birth recurrence. *American Journal of Obstetrics and Gynecology, 217*, 480.e1–480.e9. doi:10.1016/j.ajog.2017.05.051

Soilly, A. L., Lejeune, C., Quantin, C., Bejean, S., & Gouyan, J. B. (2014). Economic analysis of the costs associated with prematurity

from a literature review. *Public Health, 128*, 43–62. doi:10.1016/j.puhe.2013.09.014

Sonek, J., Krantz, D., Carmichael, J., Downing, C., Jessup, K., Haidar, Z., . . . McKenna, D. (2018). First trimester screening for early and late preeclampsia using maternal characteristics, biomarkers, and estimated placental volume. *American Journal of Obstetrics and Gynecology, 218*, 126.e1–126.e13. doi:10.1016/j.ajog.2017.10.024

Spees, C. K., Clark, J. E., Hooha, N. H., Watowicz, R. P., & Taylor, C.-A. (2017). Dietary intake contributions of food and beverages by source and food security status in UH adults. *Journal of Nutrition Education and Behavior, 49*, 667–673.e1. doi:10.1016/j.jneb.2017.01.009

Spinelli, J., Collins-Priano, L., Van Den Heuvel, C., & Byard, R. W. (2017). Evolution and significance of the triple risk model in sudden infant death syndrome. *Journal of Paediatrics and Child Health, 53*, 112–115. doi:10.1111/jpc.13429

Stensvold, H. J., Klingenberg, C., Stoen, R., Master, D., Braelkke, K., Guthe, H. J., . . . Ronnestad, A. E. (2017). Neonatal morbidity and 1-year survival of extremely preterm infants. *Pediatrics, 139*(3), e20161821. doi:10.1542/peds.2016-1821

Stephens, A. S., Lain, S. J., Roberts, C. L., Bowen, J. R., & Nassar, N. (2016). Survival, hospitalization, and acute care costs of very and moderate preterm infants in the first 6 years of life: A population based study. *The Journal of Pediatrics, 169*, 43–62. doi:10.1016/j.jpeds.2015.10.028

Stuebe, A., Auguste, T., & Gulati, M. (2018). ACOG Committee Opinion No. 736. Optimizing postpartum care. *Obstetrics and Gynecology, 131*(5), 949–962. doi:10.1097/AOG.0000000000002633

Sultana, Z., Maiti, K., Aitken, J., Morris, J., Dedman, L., & Smith, R. (2017). Oxidative stress: Placental ageing-related pathologies and adverse pregnancy outcomes. *American Journal of Reproductive Immunology, 77*, e12653. doi:10.1111/aji.12653

Sumners, J., Ecker, J. L., & Hearns-Stokes, R. (2016). Committee opinion summary, no. 671 summary. Perinatal risks associated with assisted reproductive technology. *Obstetrics and Gynecology, 128*(3), e61–e68. doi:10.1097/AOG.0000000000001643

Susuman, A. S., Chialepeh, W. N., Bado, A., & Lailulo, Y. (2016). High infant mortality rate, high total fertility rate and very low female literacy in selected African countries. *Scandinavian Journal of Public Health, 44*, 2–5. doi:10.1177/1403494815604765

Swartz, J. J., Hainmueller, J., Lawrence, D., & Rodriquez, M. L. (2017). Expanding prenatal care to unauthorized immigrant women and the effects on infant health. *Obstetrics and Gynecology, 130*(5), 938–945. doi:10.1097/AOG.0000000000002275

Tan, H. L. E., Luu, J., Caswell, A., Holliday, E., Attia, J., & Acharya, S. (2017). Impact of new International Association of Diabetes and Pregnancy Study Groups (IADPSG) diagnostic criteria in a regional tertiary hospital in New South Wales, Australia. *Diabetes Research and Clinical Practice, 134*, 191–198. doi:10.1016/j.diabres.2017.09.016

Thompson, L. M., Levi, A. J., Bly, K. C., Ha, C., & Keirns, T. (2014). Premature or just small? Training Guatemalan birth attendants to weigh and assess gestational age of newborns: An analysis of outcomes. *Health Care for Women International, 35*, 216–231. doi:10.1080/07399332.2013.829066

Tian, Y. (2017). *Michigan stillbirth rate, 2015*. Retrieved from https://www.michigan.gov/documents/mdhhs/170517Stillbirth_2015_final_6.21.17_576451_7.pdf

Travers, C. P., Carlo, W. A., McDonald, S. A., Das, A., Bell, E. F., Ambalavan, N., . . . Higgins, R. D. (2018). Mortality and pulmonary outcomes of extremely preterm infants exposed to antenatal corticosteroids. *Journal of Obstetrics and Gynecology, 218*, 130.e1–130.e13. doi:10.1016/j.ajog.2017.11.554

Trinidad, M. C., & Wick, M. (2017). ACOG practice bulletin no. 187. Neural tube defects. *Obstetrics and Gynecology, 130*(6), e279–e290. doi:10.1097/AOG.0000000000002412

Trujillo, J., Vigo, A., Duncan, B. B., Falavigna, M., Wendland, E. M., Campos, M. A., & Schmidt, M. I. (2015). Impact of the International Association of Diabetes and Pregnancy Research Study Groups criteria for gestational diabetes. *Diabetes Research and Clinical Practice, 108*, 288–295. doi:10.1016/j.diabres.2015.02.007

United Nations. (2015). *Transforming our world: The 2030 agenda for sustainable development*. Retrieved from http://www.un.org/en/ga/search/view_doc.asp?symbol=A/RES/70/1&Lang=E

United Nations Children's Fund. (2018). *Data, antenatal care*. Retrieved from https://data.unicef.org/topic/maternal-health/antenatal-care

United Nations Population Fund-United Nations Children's Fund. (2017, June). *UNFPA-UNICEF global programme to accelerate action to end child marriage: Progress report 2016*. Retrieved from https://www.unicef.org/protection/files/ChildMarriage-Global-DonorReport-v7.pdf

U.S. Department of Health and Human Services. (n.d.). *Trends in teen pregnancy and childbearing*. Retrieved from https://www.hhs.gov/ash/oah/adolescent-development/reproductive-health-and-teen-pregnancy/teen-pregnancy-and-childbearing/trends/index.html

Waldenström, U., Cnattingius, S., Vixner, L., & Norman, M. (2017). Advanced maternal age increases the risk of very preterm birth, irrespective of parity: A population based register study. *British Journal of Obstetrics and Gynaecology, 124*, 1235–1244. doi:10.1111/1471-0528.14368

Walker, D. S., Edwards, W. E. R., & Herrington, C. (2016). Fetal alcohol spectrum disorders: Prevention, identification, and intervention. *The Nurse Practitioner, 41*(8), 28–34. doi:10.1097/01.NPR.0000488709.67444.92

Walker, N., & Gan, J.-H. (2017). Prolonged pregnancy. *Obstetrics, Gynecology, and Reproductive Medicine, 27*(10), 311–315. doi:10.1016/j.ogrm.2017.07.005

Wallace, J. L., Aland, K. L., Blatt, K., Moore, E., & DeFranco, E. A. (2017). Modifying the risk of preterm birth: Influence of trimester specific changes in smoking behaviors. *American Journal of Obstetrics & Gynecology, 216*, 310.e1–e8. doi:10.1016/j.ajog.2016.11.1034

Wang, R., Metayer, C., Morimoto, L., Wiemels, J. L., Yang, J., DeWan, A. T., . . . Ma, X. (2017). Parental age and risk of pediatric cancer in the offspring: A population-based record-linkage study in California. *American Journal of Epidemiology, 186*(7), 843–856. doi:10.1093/aje/kwx160

Warren, J. L., Son, J.-Y. Pereira, G., Leaderer, B. P., & Bell, M. L. (2018). Investigating the impact of maternal residential mobility on identifying critical windows of susceptibility to ambient air pollution during pregnancy. *American Journal of Epidemiology, 187*(5), 992–1000. doi:10.1093/aje/kwx335

Waters, T. P., Dyer, A. R., Scholtens, D. M., Dooley, S. L., Herer, E., Lowe, L. P., . . . Catalano, P. M. (2016). Maternal and neonatal morbidity for women who would be added to the diagnosis of GDM using the IADPSG criteria: A secondary analysis of hyperglycemia and adverse pregnancy outcomes study. *Diabetes Care, 39*(12), 2204–2210. doi:10.2337/dc16-1194

Welton, M., Rodriguez-Lainz, A., Loza, O., Brodine, S., & Fraga, M. (2016). Use of lead-glazed ceramic ware and lead-based folk remedies in a rural community of Baja California, Mexico. *Global Health Promotion, 25*(1), 6–14. doi:10.1177/1757975916639861

Wesselink, A. K., Rothman, K. J., Hatch, E. E., Mikkelsen, E. M., Sorensen, H. T., & Wise, L. A. (2017). Age and fecundability in a North American preconception cohort study. *American Journal of Obstetrics and Gynecology, 217*, 667.e1–667.e8. doi:10.1016/j.ajog.2017.09.002

Westerneng, M., Witteveen, A. B., Warmelink, J. C., Spelten, E., Honig, A., & de Cock, P. (2017). Pregnancy-specific anxiety and its association with background characteristics and health-related behaviors in a low-risk population. *Comprehensive Psychiatry, 75*, 6–13. doi:10.1016/j.comppsych.2017.02.002

Wilhoit, L. F., Scott, D. A., & Simecka, B. A. (2017). Fetal alcohol spectrum disorders: Characteristics, complications, and treatment. *Community Mental Health Journal, 53*, 711–718. doi:10.1007/s10597-017-0104-0

Witteveen, T., Van Den Akkar, T., Zwart, J. J., Bloemenkamp, K. W., & Van Roosmalen, J. (2016). Severe acute maternal morbidity in multiple pregnancies: A nationwide cohort study. *American Journal of Obstetrics and Gynecology, 214*(5), 641.e1–641.e10. doi:10.1016/j.ajog.2015.11.003

Wong, V. W., Lin, A., & Russell, H. (2017). Adopting new World Health Organization diagnostic criteria for gestational diabetes: How the

prevalence changes in a high-risk region in Australia. *Diabetes Research and Clinical Practice, 129*, 148–153. doi:10.1016/j.diabres.2017.04.018

World Health Organization. (2013). *Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy*. Retrieved from http://apps.who.int/iris/bitstream/handle/10665/85975/WHO_NMH_MND_13.2_eng.pdf;jsessionid=337969058560FD3DC04F05700027B356?sequence=1

World Health Organization. (2014). *Every newborn action plan. An action plan to end preventable deaths*. Retrieved from http://www.who.int/maternal_child_adolescent/newborns/every-newborn/en

World Health Organization. (2016a). *Sexual and reproductive health. New guidelines on antenatal care for a positive pregnancy experience*. Retrieved from http://www.who.int/reproductivehealth/news/antenatal-care/en

World Health Organization. (2016b). *Trends in maternal mortality: 1990 to 2015*. Retrieved from https://apps.who.int/iris/bitstream/handle/10665/194254/9789241565141_eng.pdf;jsessionid=13AE83BFDDAED66B2F20CD5802850DE3?sequence=1

World Health Organization. (2018a). *Fact sheet: Adolescent pregnancy*. Retrieved from http://www.who.int/news-room/fact-sheets/detail/adolescent-pregnancy

World Health Organization. (2018b). *Immunization, vaccines, and biologicals*. Retrieved from https://www.who.int/immunization/en/

World Health Organization. (2018c). Maternal morbidity fact sheet. 16 February 2018. Retrieved from http://www.who.int/en/news-room/fact-sheets/detail/maternal-mortality

World Health Organization. (2018d). WHO recommendations on antenatal care for a positive pregnancy experience. Retrieved from https://www.who.int/reproductivehealth/publications/intrapartum-care-guidelines/en/

Yamamoto, J., Kallas-Koeman, M. M., Butalia, S., Lodha, A., & Donovan, L. E. (2017). Large-for-gestational-age (LGA) neonate predicts a 2.5-fold increased odds of neonatal hypoglycaemia in women with type 1 diabetes. *Diabetes/Metabolic Research and Reviews, 33*, e2824. doi:10.1002/dmrr.2824

Yamamoto, S., & Premji, S. (2017). The role of body, mind, and environment in preterm birth: Mind the gap. *Journal of Midwifery and Women's Health,* 62, 696–705. doi:10.1111/jmwh.12658

Yates, G., & Bass, C. (2017). The perpetrators of medical child abuse (Munchausen syndrome by proxy)–A systematic review of 796 cases. *Child Abuse and Neglect,* 72, 45–53. doi:10.1016/j.chiabu.2017.07.008

Yen, A. M.-F., Boucher, B. J., Chiu, S. Y.-H., Fann, J. C.-Y., Chen, S. L.-S., Huang, K.-C., & Chen, H.-H. (2016). Longer duration and earlier age of onset of paternal betel chewing and smoking increases metabolic risk in human offspring, independently, in a community-based screening program in Taiwan. *Circulation, 134*(*5*), 392–404. doi:10.1161/CIRCULATIONAHA.116.021511

Yingwattanakul, P., & Moschis, G. P. (2017). Life course perspectives on the onset and continuity of preventative healthcare behaviors. *Journal of Primary Prevention, 38*, 537–550. doi:10.1007/s10935-017-0482-7

Zhao, L., McCauley, K., & Sheeran, L. (2017). The interaction of pregnancy, substance use, and mental illness on birthing outcomes in Australia. *Midwifery, 54*, 81–88. doi:10.1016/j.midw.2017.08.007

CHAPTER 3

Resuscitation and Stabilization of the Newborn and Infant

Gail A. Bagwell

INTRODUCTION

The vulnerable and sick infant requires the healthcare professional to quickly assess and take action when signs of cardiac or respiratory depression are present. This chapter begins with a discussion of risk factors that predispose the newborn to cardiorespiratory depression followed by a description of the actions to be taken to avoid this depression or to alleviate the symptoms and reverse a downward spiral and concludes with a short discussion on the stabilization of the ill neonate.

CAUSES OF CARDIORESPIRATORY DEPRESSION IN THE NEWBORN

The combined effects of numerous maternal, fetal, and intrauterine factors determine the condition of an infant at birth (some of these factors are listed in Table 3.1). Although some of these factors emerge only during labor and delivery (e.g., cord prolapse), most arise during gestation (e.g., placenta previa) or even before conception (e.g., maternal diabetes). Regardless of the site or time of origin, the influence of each of these problems can manifest as cardiorespiratory depression in the newborn.

To provide effective care, the nurse must be able not only to recognize potential risk factors but also to understand the ways in which they disrupt cardiorespiratory function. Ideally, the healthcare professional determines that cardiorespiratory depression may occur and is thoroughly prepared to intervene. Although many risk factors come into play, the underlying pathogenic processes can be divided into six major categories. The mnemonic TAMMSS can be used as a simple but effective means of remembering these etiologic groups:

T Trauma
A Asphyxia (intrauterine)
M Medication
M Malformation
S Sepsis
S Shock (hypovolemia)

Trauma

Traumatic injury to the central or peripheral nervous system of the newborn is an uncommon occurrence that can result in immediate

TABLE 3.1

CONDITIONS ASSOCIATED WITH ASPHYXIATION OF NEWBORNS

Source of Problem	Conditions
Maternal	Amnionitis; anemia; gestational or insulin-dependent diabetes; gestational hypertension; preeclampsia or eclampsia; chronic maternal hypertension; maternal cardiac, pulmonary, renal, thyroid, neurologic, or genetic disease; maternal deformities; hypotension; infection; polyhydramnios; oligohydramnios; drug therapy such as magnesium sulfate; adrenergic agonists; maternal substance abuse; no prenatal care; mother older than 35 years of age; previous fetal or neonatal death
Uterine	Preterm labor, prolonged labor, premature rupture of membranes, multiple gestation, breech or other abnormal fetal presentation, precipitous delivery, uterine tachysystole with fetal heart rate changes
Placental	Placenta previa, abruption placentae, any second or third trimester bleeding, other significant intrapartum bleeding, placental insufficiency, postterm gestation
Umbilical	Cord prolapse, entanglement, compression, or rupture
Fetal	Category 2 or 3 fetal heart rate patterns, cephalopelvic disproportion, size date discrepancy, macrosomia, prematurity, intrauterine growth retardation, congenital abnormalities, fetal anemia or isoimmunization, erythroblastosis fetalis, intrauterine infection, decreased fetal activity, narcotics administered to the mother within 4 hours of delivery, meconium-stained fluid
Iatrogenic	Mechanical (difficult forceps or vacuum delivery), emergency C-section, drugs–general anesthesia

or delayed respiratory depression. Because the skull is incompletely mineralized and has open sutures, it can undergo considerable distortion without fracture. The underlying membranes and vessels are, however, much less resilient and are easily stretched or torn (subgaleal hemorrhage) if overly compressed, particularly if the pressure is abruptly applied. Similarly, forced traction or torsion of the neck during delivery may damage the spinal cord or the phrenic nerve, with consequent paralysis of the diaphragm or brachial plexus nerve group. An unusually long and difficult delivery, multiple gestation, abnormal presentation (especially breech), cephalopelvic disproportion (secondary to macrosomia or a small or contracted pelvis), shoulder dystocia, or rapid extraction by forceps or vacuum extraction (as may be required for fetal distress) are frequently involved. Despite their generally low birth weight, premature infants also may be at risk because of the unusual compliance of their skulls.

Asphyxia (Intrauterine)

The most common cause of cardiorespiratory depression at birth is fetal hypoxia and asphyxia. Any condition that reduces oxygen delivery to the fetus may be the cause. Such conditions include maternal hypoxia (from hypoventilation and hyperventilation, respiratory or heart disease, anemia, postural hypotension), maternal vascular disease that results in placental insufficiency (from preexisting or pregnancy-induced diabetes, primary or pregnancy-induced hypertension), and accidents involving the umbilical cord (compression, entanglement, or prolapse). Postterm pregnancies also are at risk, perhaps because of placental aging and progressive placental insufficiency. An asphyxia episode occasionally may trigger the passage and aspiration of meconium in utero for term and postterm infants.

Medication

Pharmacologic agents given to the mother during labor and delivery may affect the fetus both directly and indirectly. Indirectly, these agents may cause maternal hypoventilation and hypotension or adversely affect placental perfusion. Hypnotic, analgesic, or anesthetic drugs may depress maternal respirations, resulting in reduced oxygen intake and delivery to the tissues and organs, including the uterus and placenta. Anesthetic agents, because of their effect on the sympathetic nervous system, may also cause peripheral vasodilation, diminished cardiac output, and hypotension with decreased placental perfusion. Narcotic analgesics, which rapidly cross the placenta, may directly depress the neonatal respiratory drive. Oxytocin (Pitocin), on the other hand, may cause uterine hyperstimulation and shorten placental perfusion time. Each of these conditions places the fetus at greater risk of fetal hypoxia and asphyxia. In addition, prescription and nonprescription medications, herbs, and essential oils that the mother may take prior to delivery may also affect the fetus. Many street drugs, especially opiate derivatives, are known to cause infants to deliver prematurely, to be small for gestational age, to have congenital anomalies as well as cause infants to have respiratory depression on delivery.

Malformation

Infants may have any of a vast array of congenital anomalies, but the ones that cause the most problems during the first few minutes of life are those associated with facial or upper airway deformities and conditions that lead to pulmonary hypoplasia. Many of these conditions can be diagnosed through antenatal ultrasonographic examinations and other screening techniques, but suspicion also should be raised if oligohydramnios or polyhydramnios is reported.

Oligohydramnios is seen with prolonged rupture or leakage of membranes and neonates with renal agenesis or dysplasia or urethral obstruction. If fluid is lost or diminished, the developing fetal structures may be compressed, leading to characteristic Potter facies (including micrognathia) or pulmonary hypoplasia. Polyhydramnios is seen in infants with impaired swallowing ability (as in anencephaly, neuromuscular disorders), in those with real or functional obstruction high in the gastrointestinal tract (as with esophageal atresia), and in those with profuse leakage of cerebrospinal fluid (as in neural tube defects), which contributes to the volume of amniotic fluid. Polyhydramnios is also noted with diaphragmatic hernia and hydrops fetalis.

Sepsis

The fetus may acquire bacterial or viral agents from infected amniotic fluid, from maternal blood crossing the placenta, or from direct contact on passage through the birth canal. An infant is especially susceptible to infection if born prematurely (because these infants are relatively immunocompromised) or if born to a mother who had a premature rupture of membranes or a history of infection or chorioamnionitis. If infection is acquired in utero, the lungs tend to be heavily involved, and the alveoli may be filled with exudate. The infant may be apneic at birth, may be slow to establish a spontaneous and regular breathing pattern, or may show frank signs of respiratory distress.

Shock (Hypovolemia)

Most of the blood lost during delivery is from the maternal side of the placenta; therefore, it is of no consequence to the newborn. Blood loss from the fetal side of the placenta as a result of abruptio placenta or placenta previa can, however, lead to acute hypovolemia and cardiovascular collapse. Normally the umbilical cord is unusually strong, but ruptures are possible if cord tension increases suddenly, as in a precipitous delivery, or if the vessels are superficially implanted in the placenta (velamentous insertions). In rare cases acute hypovolemia may occur without frank hemorrhage. With severe cord compression, for example, blood flow to the fetus is impeded. The umbilical arteries, however, are much more resistant to compression and continue to pump blood back to the placenta. In this case, the effects of hypovolemia and asphyxia may be superimposed. Infants with chronic blood loss (as in fetal–maternal hemorrhage or twin-to-twin transfusions) are generally asymptomatic immediately after delivery.

PREPARATION FOR DELIVERY

While the majority of deliveries will result in a healthy neonate where delayed cord clamping can occur and then the infant can go immediately to the mother's chest for skin to skin care, healthcare professionals must always be prepared for a problem to arise. The general consensus is that approximately 10% of all births will require some assistance to begin breathing at birth and only 1% require compressions and medications.

Quality and Safety: The success of resuscitative efforts depends on multiple factors: (a) anticipation of the need, (b) the presence of trained personnel, (c) ready availability of necessary equipment and supplies, and (d) strong communication and teamwork. The most competent personnel and the finest equipment are useless if they are not present in the delivery room. Frantic calls for assistance or a scavenger hunt for equipment

should never occur; they needlessly delay intervention and can compromise the patient's outcome.

The antepartum and intrapartum history of each pregnant woman must be carefully reviewed to identify those at risk of delivering a depressed infant. Especially worrisome is a fetus that clinically demonstrates the effects of asphyxia (i.e., an indeterminate/abnormal fetal heart rate pattern, particularly bradycardia and persistently minimal or loss of fetal heart rate variability; acidosis, as determined by fetal scalp blood sampling; or meconium-stained amniotic fluid).

Personnel

Although most risk factors can be identified at some time during the pregnancy, many may not become apparent until birth. Delivery through meconium-stained amniotic fluid and unexpected diaphragmatic hernia are just two cases in point. Consequently, at least one person competent in neonatal resuscitation should be present at every delivery. In addition, each institution that delivers babies needs to have a plan in place on how to mobilize a full neonatal resuscitation team in an emergency such as the delivery of a depressed newborn (Weiner, 2016; Wyckoff et al., 2015).

When a team is required, the role each member is to play in the resuscitative effort should be predetermined, including the head of the team. The head of the team, who has a complete set of resuscitation skills, will be the one to position the baby, open the airway and intubate the trachea if necessary, and evaluate and direct the resuscitation efforts. A second person will assist with positioning, suctioning, and drying, as well as giving oxygen and positive pressure ventilation (PPV). A third person is responsible for monitoring the heart rate and for initiating chest compressions, if needed. If intravenous (IV) medications are required, two additional individuals are needed, one to catheterize the umbilical vein and administer the drugs and the other to pass equipment and prepare the medications. The person who passes the equipment and prepares the medications may also be responsible for documenting the resuscitation process, but a sixth person is preferable to do this because minute-to-minute notations must be made. The individual delivering the baby is not considered part of this resuscitative team, as his or her main concern is the mother.

Quality and Safety: **All team members should be trained in neonatal resuscitation via an evidence-based program such as the American Academy of Pediatrics (AAP) Neonatal Resuscitation Program (NRP) for high-resource areas or in-patient facilities or Helping Babies Breathe (HBB) for low-resource areas or rural community settings.** Both the programs emphasize the importance of strong communication skills of team members for the team to be effective and provide the highest level of care possible.

Equipment and Supplies

A newly born infant is predisposed to heat loss (particularly evaporative and radiant losses), and, if unprotected, can quickly become cold stressed. The consequences of such stress include hypoxemia, metabolic acidosis, and rapid depletion of glycogen stores with hypoglycemia. All are conditions that may exacerbate asphyxia and thus complicate resuscitation. Clearly, measures to prevent hypothermia must be part of any resuscitative effort. The delivery room should be kept warm, and the radiant bed should be preheated, if possible. Prewarming of linens, towels, and caps or other head coverings is also helpful.

For a premature baby of less than 32 weeks' gestation, the use of a food-grade polyethylene bag or wrap up to the baby's neck, without drying, in addition to a warm cap will reduce convective and evaporative heat loss. The use of the polyethylene bag or wrap will also help maintain the infant's body temperature in the delivery room as well as decrease hypernatremia at 24 to 48 hours of life due to transepidermal water loss. In addition, it has been found that a delivery room of at least 26°C assists with maintaining a premature infant's (<32 weeks' gestation) body temperature in combination with the use of a polyethylene bag or wrap. Because of this finding, all delivery room temperatures should be at least 26°C or 78.8°F when delivering a baby less than 32 weeks' gestation. Other interventions for preventing heat loss in infants less than 32 weeks' gestation are the use of a prewarmed hat and a thermal mattress (Perlman et al., 2015; Weiner, 2016; Wyckoff et al., 2015).

Possible exposure to blood and body fluids is of particular concern in the delivery room. Gloves, gowns, masks, and protective eyewear should be worn in the delivery room as procedures are likely to generate droplets or splashes of blood or other body fluids.

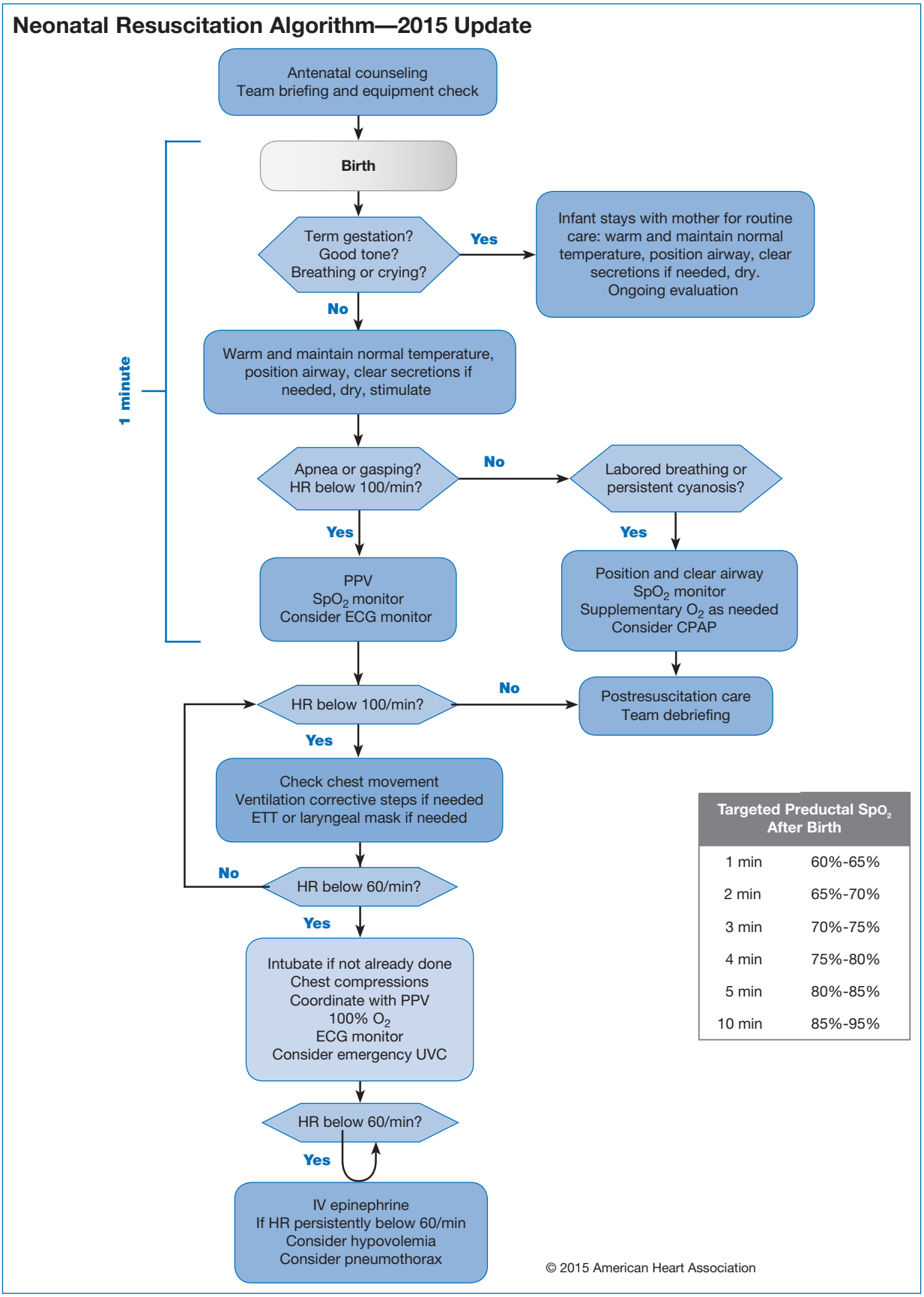
The additional equipment and supplies needed to carry out a full resuscitation (Box 3.1) should be checked as part of the daily routine. Small supplies should be organized according to frequency of use and may be displayed on a wall board, kept in the radiant warmer (if there is sufficient drawer space), or stored in a cart or specially designed tackle box. Breakaway security clips may be used to safeguard materials when they are not in use, but foolproof or locking closures that require a key or a code are not appropriate in delivery rooms, birthing rooms, or nurseries. A bedside table or flat surface (other than the bed) should be within reach to provide space for catheter trays and medication preparation.

As the delivery nears, the team should be assembled with the identified team leader. A pre-resuscitation briefing should occur, and all equipment and supplies should be double-checked to ensure they are in working order. Having an organized routine of checking the equipment will ensure that all equipment is present and in working order. Hospital infection control policies dictate how far in advance packaged supplies can be opened, connected to tubing, and otherwise prepared. A backup or duplicate set of materials should be maintained in case of equipment failure, contamination, or multiple births. All items used should be restocked as soon as possible after the resuscitation.

Good Communication and Teamwork

Communication and teamwork are behavior skills that are essential to a successful neonatal resuscitation. The best clinicians working together in resuscitation will not work effectively together if they do not possess the skills to communicate and coordinate with each other. Learning to communicate and assign tasks is as essential to a neonatal resuscitation as the ability to perform bag/mask ventilation or cardiac compressions. Key behavioral skills that are needed during a resuscitation are know your environment, use all information available, anticipate and plan, clearly identify the team leader, communicate effectively, delegate the workload optimally, allocate time wisely, use resources wisely, call for additional help when needed, and maintain professional behavior (Weiner, 2016).

For the majority of healthcare professionals, these behavioral skills do not come naturally in an emergency situation, so practicing these skills along with technical skills, such as bag/mask ventilation, on a regular basis is important. While the AAP only requires a healthcare provider to take the NRP course every 2 years, studies have shown that skills, knowledge, and self-confidence were improved when training occurred at least every 6 months or more frequently in a simulation lab or at the bedside (Matterson et al., 2018; Mosley & Shaw, 2013; Surcouf, Chauvin,



Targeted Preductal SpO_2 After Birth	
1 min	60%-65%
2 min	65%-70%
3 min	70%-75%
4 min	75%-80%
5 min	80%-85%
10 min	85%-95%

FIGURE 3.1 American Heart Association Neonatal Resuscitation Algorithm (2015).

CPAP, continuous positive airway pressure; ETT, endotracheal tube; HR, heart rate; IV, intravenous; PPV, positive pressure ventilation; UVC, umbilical venous catheter.

Source: With permission from American Heart Association. (n.d.). *Guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Part 13: Neonatal resuscitation.* Retrieved from https://eccguidelines.heart.org/index.php/circulation/cpr-ecc-guidelines-2/part-13-neonatal-resuscitation/?strue=1&id=2

Box 3.1

EQUIPMENT AND SUPPLIES NEEDED FOR FULL RESUSCITATION

Thermoregulation

- Radiant warmer—preheated or other heat source
- Temperature probe and probe cover
- Warm towels, blankets, and cap
- Warm delivery room

Suction Equipment

- Bulb syringe
- Mechanical suction device set at 80–100 mmHg
- Suction tubing
- Suction catheters (5 or 6 French, 8 French, 10 French, 12 French, or 14 French)
- Meconium aspirator
- 8 French feeding tube and 20-mL syringe

Bag and Mask Equipment

- Device for delivering positive pressure ventilation, capable of delivering 90%–100% oxygen
- Face masks, newborn and premature sizes (cushioned rim masks preferred)
- Oxygen and compressed air source
- Oxygen blender set to 21% (21%–30% for infants <35 weeks' gestation)
- Flowmeter (flow rate up to 10 L/minute) and oxygen tubing to provide free-flow oxygen
- Pulse oximeter with sensor
- O_2 saturation table

Intubation Equipment

- Laryngoscope with straight blades, No. 0 (preterm) and No. 1 (term)
- Extra bulbs and batteries for laryngoscope
- ET tubes—2.5, 3.0, 3.5, and 4.0 mm internal diameter
- Stylet (optional)
- Scissors
- Tape or securing device for ET tube
- Tape measure or ET tube depth table
- CO_2 detector or capnograph
- Laryngeal mask airway—size 1.0 and 5 mL syringe

Medications

- Epinephrine 1:10,000 (0.1 mg/mL)
- Normal saline for volume expansion and flushes
- 10% Dextrose (optional)
- Syringes—1, 3, 5, 20, and 60 mL sizes

Umbilical Vessel Catheterization Supplies

- Sterile gloves
- Scalpel or scissors
- Antiseptic prep solution
- Umbilical tape
- Umbilical catheters—3.5, 5 French
- Three-way stopcock
- Syringes—1, 3, 5, 10, 20, 50 mL
- Needles—25, 21, 18 gauges—or puncture device for needleless system

(*continued*)

Box 3.1 (*continued*)

Miscellaneous

- Gloves and appropriate personal protection
- Firm, padded resuscitation surface
- Clock with second hand (timer optional)
- Stethoscope (neonatal head preferred)
- Tape, ½ or ¾ inch
- Cardiac monitor and electrodes
- Oropharyngeal airways—0, 00, 000 sizes or 30, 40, and 50 mm lengths

For Very Preterm Babies

- Size 00 laryngoscope blade (optional)
- Reclosable, food-grade plastic bag (1-gallon size) or plastic wrap
- Chemically activated warming pad
- Delivery room temperature increased to 78°F–82°F
- Transport incubator to maintain baby's temperature during move to the nursery

Source: Adapted from Weiner, G. M. (Ed.). (2016). *Textbook of neonatal resuscitation* (7th ed.). Elk Grove, IL: American Academy of Pediatrics, and American Heart Association.

Ferry, Yang, & Barkemeyer, 2013). Simulation-based training on a regular basis should be done at all facilities to help healthcare providers maintain their cognitive, technical, and behavioral skills.

GENERAL CONSIDERATIONS

The two goals of resuscitation are (1) to remove or ameliorate the underlying cause of asphyxia and (2) to reverse or correct the associated chain of events (hypoxia, hypercarbia, acidosis, bradycardia, and hypotension). To achieve these ends, resuscitation management should be centered on attempts to expand, ventilate, and oxygenate the lungs, with cardiac assistance provided as necessary. Intervention must, however, be specific to each infant in extent and form and must be determined by appropriate assessment.

The Apgar score provides a shorthand description of the neonate's condition at specific intervals after birth and may be useful as a rough prognostic indicator of long-term outcome; however, it does have limitations. Although it is a quantitative tool, the scoring often is subjectively or retrospectively applied. It often is poorly correlated with other indicators of well-being, such as cord pH. Its usefulness is suspect with extremely preterm infants, who may have poor respiratory drive and who may be relatively hyporeflexive and hypotonic because of immaturity rather than distress. Finally, waiting until the first Apgar score is assigned at 1 minute of age causes unnecessary delay in care. For these reasons, the Apgar score should not be used to determine the need for or course of resuscitation, but it may have a role in the determination of the continuation of resuscitation (Perlman et al., 2015; Weiner, 2016).

Delayed cord clamping for greater than 30 seconds in vigorous term and preterm newborns that have an intact placental circulation has been shown to be advantageous to the newborn. Preterm newborns who had delayed cord clamping for 30 to 60 seconds had higher blood pressure, higher blood volume, decreased need for blood transfusion, and decreased incidence of intraventricular hemorrhages (IVH) and necrotizing enterocolitis (AAP, 2017; ACOG, 2017). For the term neonate, the advantages are less incidence of iron-deficiency anemia, although it may increase the amount and severity of jaundice (AAP, 2017; ACOG, 2017). The determination of whether delayed cord clamping should occur in the delivery room should be discussed between the obstetrical and neonatal providers prior to the delivery of the infant. The condition of the neonate at birth will determine if delayed cord clamping can occur. More information on delayed cord clamping is discussed in Chapter 13, Hematologic System.

As soon as the need for resuscitation is determined, the initiation of resuscitation is based on two signs: respirations and heart rate. Heart rate is the most sensitive indicator of resuscitation efforts. In the review of literature it was found that the use of a 3-lead electrocardiography (ECG) was more accurate than auscultation, palpation of the umbilical cord, or the use of a pulse oximeter in determining the neonate's heart rate (Kamlin, O'Donnell, Everest, Davis, & Mosely, 2006; van Vonderen et al., 2015). The authors of the studies demonstrated that healthcare providers could not palpate the umbilical cord accurately or that they underestimated the heart rate when auscultating the heart with a stethoscope. In addition, the 3-lead ECG was quicker and more reliable than the pulse oximeter (Dawson et al., 2013; Katheria, Rich, & Finer, 2012; Mizumoto et al., 2012; van Vonderen et al., 2015).

As the resuscitation progresses, oxygenation is added to the signs that are assessed to determine the effectiveness of the resuscitation. Visual assessment of cyanosis is not a reliable method for judging a neonate's color or oxygen saturation in the delivery room and should not be used. In addition, with studies demonstrating that hyperoxia is as detrimental as hypoxia at the cellular and functional levels, the most accurate way of determining a neonate's oxygen saturation is to use a pulse oximeter in the delivery room (Weiner, 2016). When placing a pulse oximeter, place it on the neonate's right hand or wrist, as preductal values are higher than postductal values. Always place the probe on the neonate prior to connecting the probe to the machine to produce quicker and more reliable values.

As soon as the infant has been positioned under a radiant warmer, thoroughly dried, airway cleared if necessary and stimulated, the assessment of these three signs is to occur at 30-second intervals until compressions began, at which time assessment will

occur in 60 second intervals and interventions are carried out as needed. The basics of neonatal resuscitation are as easy as ABCD: *airway, breathing, circulation, and drugs*. These are the critical elements of any resuscitative effort.

Airway Control

Positioning. Airway control is a fundamental prerequisite for effective oxygenation and ventilation. To achieve this, the infant should be placed in a flat supine position unless there is spinal deformity; then the neonate would be placed in a side-lying position. The practice of placing the infant in a slight head-down tilt (Trendelenburg position) has been abandoned. This maneuver historically was used under the presumption that fluids from the lower extremities would be redistributed to the intrathoracic compartment. Studies with healthy adults in the Trendelenburg position have demonstrated improvement, albeit transient (lasting <10 minutes), in the stroke volume of the heart, but they have also indicated that a tilt as slight as 10° may cause blood to pool in the dependent cerebrovascular bed. Infants have only a limited ability to increase the stroke volume of their heart but are at greater risk than older children and adults for intraventricular hemorrhages secondary to rupture of the vulnerable micro-vessels of the germinal matrix; consequently, the potential benefit, if any, of the head-down tilt position is not believed to be worth the risk.

Once the infant is in the supine position, the neck is placed in a neutral or slightly extended *sniffing* position that aligns the posterior pharynx, larynx, and trachea (Weiner, 2016; Wyckoff et al., 2015). Compared with the adult tongue, an infant's tongue is relatively large in proportion to the mouth, and this slight extension moves the tongue and epiglottis away from the posterior pharyngeal wall and opens the airway. Care must, however, be taken to avoid full extension, which reduces the circumference of the airway and increases airway resistance. The reasonably safe extension posture appears to be no more than 15° to 30° from neutral. An oral airway should be placed if the tongue is unusually large (as in the Beckwith–Wiedemann syndrome) or if the chin is unusually small, causing posterior displacement of the tongue (as in the Pierre Robin sequence or the Potter association). Because newborns also have a relatively large head in comparison with the chest and tend naturally to fall into a flexed position, a shoulder roll made of a blanket or small towel may be used to raise the chest and align the cervical vertebrae. This roll may be particularly helpful if the occiput is exaggerated in size by molding, edema, or prematurity. If these procedures fail to provide an unobstructed airway, the placement of a laryngeal mask airway (LMA) or intubation is indicated (Weiner, 2016).

Suctioning. Routine suctioning of neonates on the perineum was a standard of care for all deliveries whether the amniotic fluid was clear or meconium stained. There was no evidence to support this practice so routine intrapartum oropharyngeal and nasopharyngeal suctioning for babies born with either clear or meconium-stained amniotic fluid was discontinued in 2011 as a recommendation for neonates at birth. After delivery, the infant is placed on the warming bed, quickly dried and positioned, and the airway is cleared by wiping the nose and mouth with a towel or by suctioning with a bulb syringe, or suction catheter if necessary. Increasing amounts of evidence show that suctioning, either bulb or mechanical, of the nasopharynx can create bradycardia during resuscitation; therefore, in 2010 the recommendations for suctioning (including bulb suction) immediately following birth changed. Suctioning is now reserved for only those neonates who have an obvious obstruction to spontaneous breathing or for those babies requiring PPV (Weiner, 2016). Because suctioning may cause inadvertent stimulation and gasping, the mouth should always be suctioned before the nose, *M* before *N*. Mechanical suction is often mentioned as an alternative to the bulb syringe, but it generally should not be used immediately after delivery. If infants are suctioned vigorously within the first 5 minutes of life, apnea or arrhythmias may follow. These symptoms probably are due to vagal stimulation, with reflex bradycardia. If a bulb syringe can be used instead of a suction catheter, this situation can usually be avoided. If mechanical suction is required, it should be applied for no longer than 5 seconds at a time with an 8 or 10 French suction catheter and with the equipment set to produce no more than 100 mmHg (136 cm H_2O) negative pressure (Weiner, 2016). To assist with the removal of a large amount of secretions from the mouth, turn the baby's head to the side, which will allow for the secretions to pool in the baby's cheek where they will be more easily removed.

If meconium is present in the amniotic fluid and the baby is vigorous (strong respiratory effort, good muscle tone, and heart rate >100 bpm), the baby should be treated as a non-meconium baby and remain with the mother doing skin-to-skin care, although gentle bulb suctioning of the baby's mouth and nose may be needed. If meconium is present and the baby is non-vigorous (depressed respirations, decreased muscle tone, and/or a heart rate below 100 bpm), proceed with the initial steps of resuscitation. Routine direct suctioning of the trachea before beginning the steps of resuscitation to decrease the chance of the baby aspirating the meconium is no longer recommended, as there is insufficient evidence to continue the practice (Perlman et al., 2015; Weiner, 2016; Wyckoff et al., 2015).

Tactile Stimulation. In a mildly depressed infant, drying and suctioning will usually be enough stimulation to induce effective respirations. If the respiratory rate and depth are nevertheless diminished, rubbing the back, trunk, or extremities as well as slapping or flicking the soles of the feet briefly will stimulate the infant to breathe. If the infant's reflexes are intact, 10 to 15 seconds of stimulation should be sufficient to elicit a response. Longer and more vigorous methods of stimulation should be avoided. Never spend more than 30 seconds to further stimulate an infant, as it is a waste of valuable time. Remember that the first 60 seconds after birth are referred to as the *Golden Minute*, so if clearing the airway and stimulating the neonate to breathe does not result in improvement after 60 seconds, PPV should be started (Weiner, 2016).

VENTILATION AND OXYGENATION

The most important and effective action in a neonatal resuscitation is ventilation of the compromised neonate. In fact, most infants who require resuscitation can be revived with ventilation and oxygen as needed, alone. Even when more aggressive therapies are required, they ultimately are undertaken to support oxygen delivery to the tissues, either by optimizing the airway (i.e., LMA or intubation) or by supporting the heart, which *pushes* oxygen to the periphery (i.e., chest compressions, medications).

Free-Flow Administration of Oxygen

Blow-by of 100% oxygen given at delivery was a common intervention in the past, but as stated earlier, increasing numbers of research studies show that increasing the compromised neonate's oxygen saturation more quickly than a normal healthy term neonate can be toxic and detrimental to not only a preterm infant, but to term infants as well. Studies have shown that giving a neonate 100% oxygen with PPV demonstrated no advantage in improvement when compared to neonates given PPV with room air (RA),

and actually delayed the time to the first breath and/or cry in term infants. Because of the increasing evidence from randomized controlled trials and meta-analyses of the studies demonstrating the detriments of hyperoxia, such as increased incidence of chronic lung disease and changes in the cerebral blood flow, especially in preterm babies, the use of RA at the beginning of resuscitation has been recommended since 2010. If there is no improvement, however, in heart rate or oxygenation by pulse oximetry despite adequate ventilation, increasing the amount of oxygen the neonate is receiving should be considered (Perlman et al., 2015; Weiner, 2016; Wyckoff et al., 2015). An infant who is breathing spontaneously but appears cyanotic or fails to maintain its SpO_2 within the range for the age of the infant, in room air (Table 3.2), needs supplemental oxygen. The oxygen can be provided directly from the end of the oxygen tube held in a cupped hand, by a funnel or face mask attached to the tubing, by a flow-inflating ventilation bag, by a T-piece resuscitator, or by the tail of a self-inflating bag. The blender attached to a flowmeter should be set to deliver to 10 L/minute, and the tubing, funnel, or mask should be held close to the infant's face to maximize the inhaled concentration of oxygen, but not so close that pressure would build up (Weiner, 2016).

The NRP guidelines changed in 2010 to reflect the use of room air initially on both free-flow ventilation and PPV for term infants and the use of room air to 30% oxygen for preterm infants. During resuscitation, start with room air (21%) at sea level for term infants, and then, using the preductal pulse oximeter as your guide, increase your oxygen concentration as necessary to maintain the appropriate O_2 saturation for the infant's age in minutes after birth. When determining the amount of oxygen to use in preterm infants, several studies were analyzed that looked at preterm infants younger than 35 weeks' gestation who were resuscitated using either room air or oxygen concentrations of 65% or greater. The studies showed no difference in long-term outcomes of bronchopulmonary dysplasia, retinopathy of prematurity, or intraventricular hemorrhages, but because of concerns of the effects of hyperoxia the recommendation is to start with a low range of oxygen, between room air and 30%, when resuscitating the preterm infants younger than 35 weeks' gestation (Weiner, 2016; Wyckoff et al., 2015).

TABLE 3.2

TARGETED PREDUCTAL SpO_2 AFTER BIRTH

Age in Minutes	SpO_2 Range (%)
1	60–65
2	65–70
3	70–75
4	75–80
5	80–85
10	85–95

Source: Data from Weiner, G. M. (Ed.). (2016). *Textbook of neonatal resuscitation* (7th ed.). Elk Grove, IL: American Academy of Pediatrics and American Heart Association.

Ventilation

If the infant fails to obtain a normal O_2 saturation with free-flow oxygen that has been increased to 100% or shows other signs of cardiorespiratory decompensation (apnea or gasping respirations or a heart rate below 100 bpm), PPV should be instituted. Begin PPV with a pressure of 30 to 40 cm H_2O to inflate the lungs of term neonates and 20 to 25 cm H_2O for preterm neonates. You may need to adjust the pressure as needed to achieve a rising heart rate, chest expansion, and audible breath sounds. Occasionally, it may become necessary to increase the positive pressure if no improvement occurs. Positive end expiratory pressure (PEEP) has been shown to achieve lung inflation quicker, remove the fetal lung fluid more rapidly, and prevent collapse of the alveoli between breaths. When using PEEP, set the PEEP to 5 cm as this has been found to be beneficial for both term and preterm infants requiring PPV. A ventilation rate of 40 to 60 breaths/minute should be used when ventilating the newborn (Perlman et al., 2015; Weiner, 2016).

Continuous Positive Airway Pressure

The use of continuous positive airway pressure (CPAP) in the delivery room for preterm babies is a common practice to assist them to breathe. Studies have been conducted to assess the outcomes for preterm neonates who had CPAP in the delivery room versus being intubated and given PPV. Several studies have demonstrated that spontaneously breathing infants younger than 30 weeks' gestation given CPAP had reduced rates of intubation, decreased length of time on mechanical ventilation, and possibly decreased incidence of death and development of BPD with no increase in the development of air leaks or IVHs (Dunn et al., 2011; Finer et al., 2010). Taking the results of these and other studies into consideration, the recommendation now is that spontaneously breathing preterm neonates with respiratory distress may be supported initially with CPAP rather than intubation and PPV (Weiner, 2016; Wyckoff et al., 2015).

Positive Pressure Devices

Three types of ventilation devices are available for neonatal use: the self-inflating bag, the flow-inflating bag, and the T-piece resuscitator. Whichever device is used, it should have the capability of delivering an oxygen concentration between 21% and 100%.

Self-inflating bags do not require gas flow but do require a reservoir to deliver high concentrations of oxygen. Traditionally, these bags have been fitted with a pressure-release *popoff* valve preset at 30 to 40 cm H_2O to prevent overinflation of the lungs and the risk of pneumothorax. Most self-inflating bags must be squeezed to move gas through the circuit and are not capable of passive, free-flow oxygen delivery.

Flow-inflating bags, on the other hand, are closed systems and therefore must be connected to a compressed gas source. Although self-inflating bags have the advantages of being both easy to operate and gas-flow independent, flow-inflating bags provide more reliable oxygen concentrations (particularly at low flow rates), better control of inspiratory times, and a greater range of peak inspiratory pressures, as well as free-flow oxygen.

T-piece resuscitator is a mechanical device that provides flow-controlled and pressure-limited breaths. Like the flow-inflating bag, it requires a compressed gas source to operate. The peak inspiratory pressure and end expiratory pressure are set manually with adjustable controls and the breaths are delivered manually when the operator alternately occludes and opens the aperture on the tubing attached to the mask, LMA, or endotracheal tube (ET).

All three of the devices can be used to provide ventilation by mask, LMA, or ET tube. Both types of ventilation bags can be

equipped with a manometer to monitor airway pressure as well. Though a manometer is important, visualization of the chest is equally, if not more, important. The degree of chest rise should simulate that seen when a normal newborn takes an easy breath. Excessive chest rise reflects overzealous delivery of tidal volume; if there is no movement, delivery is inadequate. A self-inflating or flow-inflating bag that has a regulatory valve with a minimum volume of 200 mL and a maximum volume of 750 mL should be used in resuscitating neonates. Term newborns require only 10 to 25 mL with each ventilation (4–6 mL/kg). A bag larger than this makes delivering the correct size breath difficult (Weiner, 2016).

Methods of Ventilation

For mask ventilation, a face mask is used to provide an oxygen-enriched *microenvironment*. An anatomically shaped mask with a cushioned rim is preferred for this purpose. Because masks are available in a variety of sizes, care must be taken to select one that covers the tip of the chin, the mouth, and the nose but not the eyes. Mask ventilation is a simple, noninvasive method of oxygen delivery that can be initiated without delay but the use of a mask has disadvantages. First, it may be difficult to obtain and maintain a good seal between the mask and the infant's face, particularly around the nose. Any leakage of air results in underventilation, which is aggravated if low lung compliance or high airway resistance is a factor. The seal should be *airtight* without excessive pressure applied. Second, the mask itself has a considerable amount of dead space. Consequently, a sufficient tidal volume must be delivered to prevent accumulation and rebreathing of carbon dioxide. Masks used for neonatal resuscitation ideally should have a dead space of less than 5 mL. Finally, prolonged bag and mask ventilation may produce gastric distention from swallowed gas, which in turn impedes diaphragmatic excursions and places the infant at risk of regurgitation and aspiration. This problem can be easily avoided, however, by inserting an 8 French orogastric tube if mask ventilation continues beyond several minutes. The gastric contents should be suctioned, and the tube left in place as a vent as long as mask ventilation is provided (Weiner, 2016).

Mask ventilation suffices for most infants, but if it proves ineffective (as evidenced by poor chest rise or continuing bradycardia) or if prolonged ventilation is expected, an LMA or ET tube should be inserted. Premature infants (certainly those weighing <1,000 g) who have diminished lung compliance, immature respiratory musculature, and decreased respiratory drive may also benefit from early intubation (Weiner, 2016).

Infants suspected of having a diaphragmatic hernia, hydrops fetalis, or certain airway or gastrointestinal abnormalities also benefit from immediate intubation. Uncuffed ET tubes with a uniform internal diameter should be used. The proper tube size and depth of insertion are determined by the infant's size, by weight, gestational age, and nasal–tragus length (NTL; Table 3.3). Most neonatal ET tubes have a set of black lines (vocal cord guide) near the tip of the tube that serve as a guide for insertion. When the vocal cords are situated between the two lines, the tube should be properly positioned with its tip in the mid-trachea. In the past the distance from the mid-trachea (tube tip) to the infant's upper lip was used to determine proper tube placement, but it was not always accurate. A more accurate method for determining the proper depth of an ET tube is to measure the NTL in a neonate and add 1 cm. This method has been shown to be more accurate in both term and preterm infants. Gestational age has also been shown to be accurate in determining insertion tube depth. (Weiner, 2016).

When the tube is properly situated, the centimeter marking on the side of the tube at the level of the upper lip should be at or near NTL. Tubes with metallic markers or fiber-optic illumination at the tip may make it possible to determine the depth of the tube transdermally (i.e., by observing a circle of light on the skin or by hearing an audible signal from a transcutaneous locator instrument), but these modifications do not allow differentiation between ET intubation and esophageal intubation, and therefore offer no advantage in an emergency situation. Similarly, capnometers used during resuscitation to measure end-tidal carbon dioxide, and thus confirm tube placement in the trachea, may be inaccurate when pulmonary blood flow is poor or absent (Weiner, 2016).

TABLE 3.3

ENDOTRACHEAL TUBE SIZE AND PLACEMENT

Infant's Weight (g)	Infant's Gestational Age (weeks)	Tube Size (mm)	Insertion Depth (cm)
500–600	23–24	2.5	5.5
700–800	25–26	2.5	6.0
900–1,000	27–29	2.5	6.5
1,100–1,400	30–32	3.0	7.0
1,500–1,800	33–34	3.0	7.5
1,900–2,400	35–37	3.5	8.0
2,500–3,100	38–40	3.5	8.5
3,200–4,200	41–43	3.5 or 4.0	9.0

Sources: Data from the American Heart Association Emergency Cardiac Care Committee and Subcommittees. (1992). Guidelines for cardiopulmonary resuscitation and emergency cardiac care. VII. Neonatal resuscitation. *Journal of the American Medical Association, 268*, 2276–2281. doi:10.1001/jama.268.16.2276; Weiner, G. M. (Ed.). (2016). *Textbook of neonatal resuscitation* (7th ed.). Elk Grove, IL: American Academy of Pediatrics and American Heart Association.

Correct placement is best demonstrated by the tried-and-true methods: improved clinical signs (heart rate, improving oxygenation, and activity), symmetric chest rise, bilateral and equal breath sounds (as auscultated in the axillae), and fogging of the tube on exhalation. Air should not be heard entering the stomach, and the abdomen should not be distended. If any doubts exist, tube placement can be checked by repeated laryngoscopy; the tube should be clearly seen passing through the glottic opening (Weiner, 2016).

ET intubation is the definitive technique for airway management and ventilation. Agility and accuracy in placement, however, require continual practice. Also, many hospital personnel are restricted by policy or statute from learning or using this skill. The LMA, which was approved by the U.S. Food and Drug Administration in 1991, has been enthusiastically accepted in some settings as an alternative that offers most of the advantages of intubation but does not require laryngoscopy for placement.

The LMA (Figure 3.2) is a relatively long tube with a bag connector and an inflation port at one end and an inflatable soft cuff at the other. The tube is blindly passed into the hypopharynx so that the tip of the cuff lodges in the esophageal opening. Inflated, the cuff creates a seal around the larynx. The tube then is connected

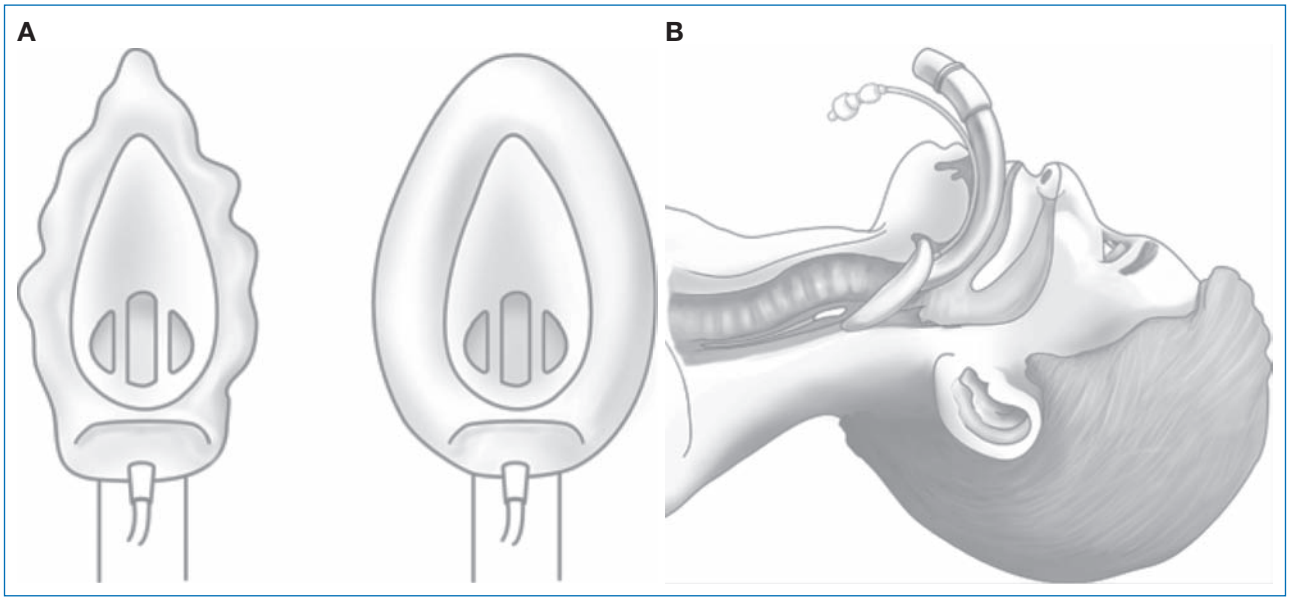


FIGURE 3.2 (A) LMA deflated for insertion (*left*) and with cuff inflated (*right*). (B) LMA in position with cuff inflated around laryngeal inlet.

LMA, laryngeal mask airway.

Source: From Efrat, R., Kadari, A., & Katz, S. (1994). The LMA in pediatric anesthesia: Experience with 120 patients undergoing elective groin surgery. *Journal of Pediatric Surgery, 29*(2), 206–208. doi:10.1016/0022-3468(94)90319-0

to a bag that delivers oxygen by ventilation through the central aperture of the laryngeal mask.

Since the LMA was approved for use by the Food and Drug Administration, research has been done to assess effectiveness in neonates. For ventilation purposes, the LMA is as effective as, but never more effective than, intubation. Placement of the LMA has been studied in neonates who are 34 weeks and older or who weigh more than 2,000 g, and case reports have shown LMAs to be an effective alternative when mask ventilation and intubation were unsuccessful. These studies also showed that effective ventilation was achieved quickly using an LMA (Trevisanuto et al., 2004; Zanardo, Simbi, Savio, Micaglio, & Trevisanuto, 2004; Zhu, Lin, Zhang, Ye, &Yu, 2011). An advantage of LMA is that it can be placed by an registered nurse (RN), respiratory therapist (RT), or physician, making providing an airway to neonates in distress easier in facilities where a physician might not be in-house 24 hours a day. Training healthcare professionals to place an LMA can be done using a mannequin. Studies have shown it to be an effective training tool (Gandini & Brimacombe, 2004; Micaglio et al., 2006).

Situations where an LMA may be useful include those where a neonate has a congenital anomaly of the mouth, lip, or palate; anomalies of the head, neck, tongue, or pharynx; a small mandible; or when ventilation with a mask is ineffective and intubation is not feasible. A disadvantage of LMA is that even with successful placement, nearly a quarter of infants with an LMA subsequently develop airway obstruction, probably because of displacement during patient movement. The cuff provides only a low-pressure seal around the larynx, which limits the airway pressures that can be achieved during ventilation. The risks of gastric insufflation and regurgitation of gastric contents are reduced but not eliminated. Because of its size, the LMA is currently restricted to infants greater than 34 weeks' gestation or 2 kg, although there have been anecdotal reports of successful use in very small infants (1–1.5 kg). The LMA also does not provide access to the lower airway, and therefore, is not suitable for meconium removal or drug administration, nor does it preserve the airway during laryngospasm. Its usefulness in neonates who require chest compressions or with the use of emergency medication administration still needs to be assessed (Perlman et al., 2015; Weiner, 2016; Wyckoff et al., 2015).

Chest Compressions. Chest compressions are rarely required for resuscitation in the delivery room. They are performed in only 1 of every 1,000 deliveries but probably are avoidable even in most of these cases. According to some authorities, approximately one-third of the infants who received chest compressions showed biochemical evidence of asphyxia (acidemia), but the remaining two-thirds were found to have a malpositioned ET tube or inadequate ventilatory support (i.e., insufficient rate or pressure). Clearly, the airway should be reassessed, and respiratory support should be optimized before chest compressions are initiated. Assuming that these components are satisfactory, chest compressions are begun if the heart rate drops below 60 bpm after 30 seconds of *effective* ventilation (Weiner, 2016).

Chest compressions provide temporary support for circulation and oxygen delivery. Pressing on the sternum has two effects: It compresses the heart against the vertebral column, and it increases intrathoracic pressure. Both effects cause blood to be pushed out of the heart into the arterial circulation. When the sternal pressure is released, the ventricles return to their original shape, intrathoracic pressure falls toward zero, and venous blood is pulled into the heart by a suction effect (Weiner, 2016).

There are two techniques to perform chest compressions, but the thumb method is preferred by the AAP. For the thumb method, both hands encircle the chest; the fingers support the back, and the thumbs (pointing cephalad either side by side or one on top of the other, depending on the infant's size) are used to press the sternum downward. The two-finger method should only be used if the compressor's hands are too small to encircle the neonate's chest. In this method, one hand supports the back from below while two fingers of the free hand are held perpendicular to the chest and the fingertips are used to apply downward pressure on the sternum. The two-thumb method is preferred as comparative studies have shown that higher systolic blood pressure, higher diastolic

blood pressure, higher mean arterial pressure, and higher coronary perfusion pressure are generated with less external compression force when the thumb method is used. This method also has had fewer reports of trauma to the liver and other abdominal organs. Moreover, the thumb method is perhaps easier and certainly less tiring to perform. If access to the umbilicus is needed to facilitate placement of an umbilical venous catheter (UVC) for administration of emergency drugs, the compressor should move to the head of the bed next to the person providing ventilation and continue compressing with the two-thumb method, though the thumbs will now be pointing caudally (Weiner, 2016).

For both methods, the pressure is applied to the lower-third of the sternum (just below the nipple line but above the xiphoid process), where the right ventricle lies closest to the sternum. Just enough force is used to depress the sternum one-third of the anterior/posterior chest wall diameter (Weiner, 2016). To obtain the most optimal myocardial and cerebral blood flows, the downward stroke and release phases of the compression should be equal in time. This equalization is best accomplished with a smooth stroke and release rhythm.

No matter which method of compression is utilized, compressing the heart for a full 60 seconds with coordinated ventilation is essential prior to reassessing the heart rate. Studies have demonstrated that it takes at least a minute for the diastolic pressure to increase enough to begin perfusing the coronary arteries. For this reason, the most recent recommendations are for a full 60 seconds of coordinated compressions and ventilation before reassessing the heart rate (Weiner, 2016; Wyckoff et al., 2015.)

PPV with 100% oxygen must be given while chest compressions are performed. The most recent guidelines recommend interposing chest compressions with ventilations at a 3 to 1 ratio. Every fourth compression is dropped to allow delivery of a single effective breath. During the course of a full minute, 90 compressions and 30 ventilations are given (Weiner, 2016). In order to provide an adequate number of compressions without simultaneous compression/ventilation, the ventilation rate is dropped to 30 from the 40 to 60 that was done with ventilation alone.

Faster rates were recommended in the past, but they only increase the chance of administering simultaneous compressions and ventilations. Most studies indicate that simultaneous delivery increases the intrathoracic pressure to a level at which ventilation is impeded and coronary perfusion is reduced. Whether there is any effect on cerebral blood flow is equivocal, but there have been other reports of lower survival rates when simultaneous compression and ventilation were used.

Experimental techniques, such as external circulatory assist devices (e.g., mechanical *thumpers*, pneumatic vests, and abdominal binders), counterpoint abdominal compressions (e.g., cough cardiopulmonary resuscitation), and active decompression (e.g., plumber's plunger), have shown promise in animal studies. Only a few large-scale clinical trials have been conducted, however, and most of those used adults. Consequently, these methods cannot be advocated for neonatal resuscitation at this time.

Medications

Medications are rarely used in neonatal resuscitation, and if they are needed, only two are used: epinephrine and normal saline. Sodium bicarbonate and other medications are no longer used in the immediate resuscitative period but may be considered in postresuscitation care.

Epinephrine. Epinephrine is a direct-acting catecholamine with both alpha-adrenergic and beta-adrenergic effects. These effects lead to peripheral vasoconstriction, acceleration of the heart rate, and an increase in the forcefulness of cardiac contractions. The net effect is a sharp rise in blood pressure (pressor effect) and an increase in cardiac output. The marked pressor effect combined with the increased aortic diastolic pressure increases the cerebral and myocardial perfusion pressures, maintaining blood flow to these critical organs during resuscitation. Epinephrine is, therefore, considered the drug of choice with asystole or persistent bradycardia (heart rate <60 bpm) despite effective ventilation with 100% oxygen and chest compressions for 60 seconds. For newborns the recommended dosage is 0.1 to 0.3 mL/kg of 1:10,000 solution (0.01–0.03 mg/kg) intravenously (Perlman et al., 2015; Weiner, 2016; Wyckoff et al., 2015). The drug is rapidly inactivated by an enzymatically driven process known as *sulfoconjugation*, in which the active compound is conjugated with sulfate. The half-life of infused epinephrine is approximately 3 minutes. Consequently, the dose may be repeated every 3 to 5 minutes as clinically indicated.

Epinephrine ideally should be administered via the IV/UVC/IO route. Because IV/UVC placement may be difficult and time consuming during resuscitation and not all neonates are candidates for an intraosseous (IO), an initial dose of epinephrine can be given by the ET tube. Unfortunately, absorption into the circulation from the pulmonary capillary bed may be highly variable because of the low blood-flow state associated with resuscitation. In addition, much of the ET-instilled drug remains along the walls of the ET tube and in the conducting airways, with a relatively small amount finding its way into the deep absorptive surfaces of the alveoli. If epinephrine is given by the ET tube, a higher dose of 0.5 to 1 mL/kg of 1:10,000 solution (0.05–0.1 mg/kg) should be given (Perlman et al., 2015; Weiner, 2016; Wyckoff et al., 2015).

A number of steps can be taken to aid delivery when the ET route is necessary. First, to optimize blood flow to the lungs, every effort must be made to ensure that chest compressions are performed effectively. Second, epinephrine may be dispersed more quickly to deeper pulmonary tissues by following the instillation with a few forceful ventilations. When giving epinephrine via the ET tube you will be giving higher doses, which will lead to increased volume of fluid of up to 1 mL, so dilution is no longer needed (Weiner, 2016).

Although higher doses of epinephrine administered by the ET route may have a role in exceptional situations, routine IV/UVC administration of high-dose epinephrine is not recommended in newborns. Studies with adults and older children have shown a dose–response relationship, with higher doses bringing about greater improvements in coronary and cerebral blood flow; in neonates, however, the efficacy and safety of high-dose IV/UVC epinephrine have not been adequately evaluated. Most of these studies have been conducted with patients with a history of coronary artery disease who demonstrate ventricular fibrillation. Neonates, however, more commonly have bradycardia caused by hypoxia. These pathophysiologic differences prevent the extrapolation of findings. Furthermore, administration of high doses has generally been followed by a prolonged period of hypertension. Because the newborn, particularly the prematurely born, has a vascular germinal matrix, the risk may be greater for intraventricular hemorrhage. In fact, this area of the brain is most susceptible to hemorrhage when hypertension is preceded by hypotension, which is the case with resuscitation. For this reason, only the standard dose of epinephrine (0.1–0.3 mL/kg) should be given by the IV/UVC route.

Volume Expanders. Volume expanders are indicated with evidence or suspicion of acute blood loss with signs of hypovolemia. These signs include pallor despite oxygen therapy, hypotension with weak pulses despite a normal heart rate, delayed capillary

refill, and failure to respond to resuscitation (Perlman et al., 2015; Weiner, 2016; Wyckoff et al., 2015). Low hematocrit and hemoglobin concentrations are diagnostic of blood loss, but the levels may be misleadingly normal immediately after acute loss. In general, it takes about 3 hours for a sufficient amount of fluid to shift from the interstitial to the intravascular space to produce the degree of compensatory hemodilution reflected by a fall in laboratory values.

The basic requirement for any replacement solution is that the electrolyte and protein composition be roughly equivalent to that which was lost. Otherwise, an osmotic pressure gradient is created, and fluids are driven out of the capillaries into the interstitial tissue. The expansion of circulatory volume is only transient, and the infant is put at risk for secondary problems, particularly pulmonary edema. Clearly, whole blood is the fluid of choice for volume replacement, and it offers the added benefit of oxygen-carrying capacity. Fresh O-negative blood cross-matched against the mother should be used. When blood is not readily available, isotonic fluids, such as 0.9% normal saline, may also be used (Weiner, 2016). Glucose-containing fluids (e.g., D_5W or $D_{10}W$) should not be given by bolus because of the risk of profound hyperglycemia. Hyperglycemia with untreated asphyxia may aggravate metabolic acidosis.

For emergency treatment of hypovolemia, 10 mL/kg of volume expander is given slowly over 5 to 10 minutes by the IV/UVC/IO route (Weiner, 2016). Rapid infusion must be avoided, because abrupt changes in vascular pressure in the vulnerable germinal matrix capillaries place the infant (especially a preterm infant) at greater risk of intraventricular hemorrhage. The response is usually dramatic, with a prompt improvement in blood pressure, pulses, and color. If the signs of hypovolemia continue, however, a second volume replacement may be given. Persistent failure beyond this point probably indicates some degree of *pump failure*, and further improvement is not likely until cardiac function is improved.

Naloxone. In the past naloxone was used for the infant of the mother who received a narcotic analgesic for pain control during labor, as these lipid-soluble drugs rapidly cross the placenta within 2 minutes of administration and can cause neonatal respiratory depression. Peak fetal narcotic levels occur 30 minutes to 2 hours after administration to the mother. The degree and duration of depression shown by the newborn depend on the dose, the route, and how soon before delivery the drug was given. Affected neonates show decreased respiratory effort and muscle tone but typically have a good heart rate and perfusion. Due to insufficient evidence existing to evaluate the safety and efficacy of this drug in the neonate and animal studies that report complications, the use of this drug is, however, no longer recommended (Weiner, 2016).

Other Drugs. Sodium bicarbonate, dopamine, atropine, and calcium were at one time used routinely in the acute phases of neonatal resuscitation, but are no longer used as they are rarely very useful (Weiner, 2016). These drugs, along with glucose boluses, are more commonly used now in the postresuscitation period in the neonatal special care or intensive care unit.

Special Circumstances. For some infants, changes in or variations of the usual resuscitative measures are needed. Most of these infants are extremely premature, have congenital anomalies, structural defects, or conditions that compromise the cardiovascular system, such as neural tube defects, abdominal wall defects, diaphragmatic hernias, hydrops fetalis, esophageal atresia, pneumothorax, choanal atresia, and laryngeal anomalies. Resuscitative measures with these disorders are discussed in greater detail elsewhere in this textbook.

Withholding or Discontinuing Resuscitation. The law and its underlying ethical principles require that treatment be provided and continued as long as it is judged to be effective in ameliorating or correcting an underlying pathophysiologic process. Unfortunately, the data is insufficient to allow a general recommendation for how long resuscitation should be performed before continuation can be deemed futile and efforts are terminated. There is evidence that survival is unlikely at any birth weight if the Apgar score remains 0 after 10 minutes of resuscitation that has effective ventilation, coordinated with chest compressions and administration of medication, but recently some controversy has arisen with the standard of stopping resuscitation on a neonate at 10 minutes as reports have emerged regarding intact survival in infants who have received therapeutic hypothermia after birth (Perlman et al., 2015). Taking into consideration this evidence, NRP still recommends that it may be reasonable to stop resuscitation at 10 minutes if the Apgar is 0 and the resuscitative efforts have been effective, but each resuscitation should be individualized to the situation at hand (Weiner, 2016).

In the past, NRP made recommendations on when noninitiation of resuscitation would be appropriate, but the current NRP recommendation is to follow the AMA Code of Medical Ethics on determining whether noninitiation should occur. The AMA states that five factors need to be weighed to make that determination. **Emergency Alert: The five factors are (1) the chance that the therapy will succeed, (2) the risks involved with treatment and nontreatment, (3) the degree to which the therapy, if successful, will extend life, (4) the pain and discomfort associated with the therapy, and (5) the anticipated quality of life for the newborn with and without the treatment.** This information would need to be discussed with the parents prior to the delivery of the neonate, if time allows. If time does not allow or sufficient information is not available, then initiation of resuscitation should occur, and discontinuation can occur as more information becomes available (Weiner, 2016).

Although many hospitals have guidelines for withholding full resuscitation for extremely low-birth-weight infants and those with lethal anomalies, early and well-documented discussion with parents is recommended when such events are anticipated prenatally. If the event was not anticipated, great attention should be given to postmortem evaluation. Blood for chromosome examination and other pertinent laboratory work, radiographs, and an autopsy are important both for family counseling and for evaluation of the resuscitation process.

Postresuscitation Management. A successfully resuscitated neonate requires special consideration and care postresuscitation. The goal of care of stabilization is to reverse the causes of cell death and tissue injury (hypoxia, ischemia, and acidosis) and avoid or treat any exacerbating conditions (hypothermia, hypoglycemia, respiratory failure, infection). The level of neonatal care the facility is designated for and the baby's condition will help determine whether the baby should be kept at the same facility as the mother or transported from the facility to a tertiary or quarternary referral center. When transporting a baby from one facility to another, a dedicated neonatal transport team should be used to improve the outcomes for the neonate, as adult transport teams do not have the knowledge or skill set to care for the critically ill neonate.

A main goal for the newly resuscitated neonate is to prevent future complications if at all possible. A concept that originated in the emergency medicine domain and is being adopted in the neonatal domain due to improved outcomes is the *Golden Hour* concept. In trauma medicine, it was found that if a patient was treated in the first 60 minutes following the accident, then irreversible internal damage was prevented, and survival improved. In recent years this concept has been applied to the newly resuscitated neonate, especially the extremely premature neonate, and refers to the first hour of a neonate's life. Principles of the Golden Hour include the standardization of treatment protocol during and after resuscitation of the neonate, improving teamwork, maintaining thermoregulation,

the administration of glucose-containing fluids to prevent hypoglycemia, and providing appropriate developmental support for the neonate. By standardizing how care is implemented, both short- and long-term outcomes related to thermoregulation, hypoglycemia, respiratory complications, sepsis, and intraventricular hemorrhages in the neonate may be decreased (Castrodale & Rinehart, 2014; Lambeth, Rojas, Holmes, & Dail, 2016).

There are several postresuscitation programs available to train healthcare providers in the care of the recently resuscitated neonate. The Perinatal Continuing Education Program and the S.T.A.B.L.E. Program are two such programs that are available to assist healthcare professionals with learning the skills necessary to stabilize the successfully resuscitated neonate. Both programs cover fluid administration, maintenance of the glucose levels, temperature regulation, airway management, blood pressure stabilization, lab work needed, antibiotic administration, parental support, and skills acquisition in the form of simulation. All of these topics are discussed in detail in other sections of this textbook.

Documentation. No resuscitative event can go unrecorded. Unfortunately, the circumstances surrounding resuscitation are fraught with medicolegal hazards. Assessment of the infant is generally limited to the most basic measurements (respiratory rate, heart rate, and oxygenation). Immediate response may be affected by many factors unrelated to professional competence. Furthermore, the ultimate outcome may not become apparent for years. Even the best, most appropriate care can look *bad* in retrospect if documentation is incomplete or inaccurate. Yet no area of the hospital is perhaps less conducive to quality documentation than the delivery room, where a variety of professionals (nurses, physicians, and respiratory therapists) from different clinical areas (obstetrics, neonatology, anesthesiology), each with a unique perspective on the situation, are brought together in an emergency. Notes are jotted on bed linen, scrub clothes, paper towels, or anything at hand. More often than not, these brief notes are so hastily written that they are little more than a list of the medications given. When transcribed, the events may be documented in two totally separate charts, one for the mother and another for the infant. Great care must be taken with record keeping so that events and actions can be accurately reconstructed many years into the future.

Descriptive charting is most appropriate in this situation. The record should include the pertinent perinatal factors, the physical findings, the activities performed, and the infant's response, but definitive diagnoses should not be offered. It is particularly important that information concerning the pregnancy, labor, and delivery be based on fact and not hearsay. Terms such as *fetal distress* and *asphyxia* tend to take on a life of their own once they have been committed to paper, even if they are not supported by clinical evidence. It is best to record factual data, such as vital signs and blood gas determinations, without adding an interpretation. Ventilation, chest compressions, and administration of medications are essential items for documentation, but the basics should not be dismissed. It is just as important to note that attempts were made to keep the infant dry and warm.

Accurate timing of notes can be critical, because actions are judged by the minute-to-minute changes noted in the chart. A preprinted recording form or an electronic form not only helps in this regard but can also provide a structure for evaluation and decision making.

Care of the Family During Resuscitation and Stabilization

An ill neonate is a crisis for families as no one expects their baby to be born prematurely or ill. When risk factors are known that could result in a neonate needing to be resuscitated (i.e., extremely premature baby), the physician should discuss with the parents prior to the delivery, if time allows, the options available as well as survival rates of the diagnosed condition of the infant. Parents have a role in deciding the goals of the care to be delivered to their baby, but they cannot make an informed decision unless they have been presented complete and reliable information. Unfortunately, many times this type of information may not be available until after the initial resuscitation or many hours later.

During resuscitation and stabilization, healthcare professionals should keep the parents informed of what is occurring to their newborn. Parents' wishes should be honored, if appropriate. Parents may wish to be present during resuscitation efforts. Research studies have supported this presence from both a health professional's and parent's point of view (Flanders & Strasen, 2014). Some professionals are concerned about legal ramifications of the family's presence during cardiopulmonary resuscitation but the positives for both the family and healthcare team outweigh the negatives (Jones, Parker-Raley, Maxson, & Brown, 2011; Oczkowski et al., 2015).

Resuscitation and Stabilization in Low-Resource Settings

The content of this chapter has focused on resuscitation and stabilization in high-resource settings. With the globalization of healthcare and the increase in healthcare providers from developed countries traveling to countries with limited resources to teach neonatal resuscitation and care to improve neonatal survival, it has, however, become evident that our care practices do not translate to the low-resource settings where medical equipment, supplies, personnel, and even electricity are limited. Because of this, AAP joined with the United States Agency for International Development, Laerdal Global Health, Johnson & Johnson, Save the Children, and other global organizations to develop an educational program to teach healthcare providers in a limited resource setting to resuscitate and care for term and preterm newborns. The program is called Helping Babies Survive and consists of three educational suites: Helping Babies Breathe (HBB), Essential Care for Every Baby (ECEB), and Essential Care for Small Babies (ECSB). HBB was launched in 2010 and was the first of the three educational programs. The HBB goal is to give every baby born in the world a chance to take its first breath and focuses on resuscitation. Since it has been in use, HBB has been translated into over 25 languages and has helped improve neonatal care in over 80 countries. The other two educational suites, ECEB and ECSB, were launched in 2014 and 2015, respectively, to help improve care after the birth of the baby (AAP, 2018).

The HBB is an evidence-based hands-on training tool that uses the same evidence incorporated into NRP. NRP and HBB are not interchangeable courses, though, and the main difference between the two is that HBB was designed for resource limited (equipment and personnel) settings and uses different educational methodology, mentorship, and quality improvement components. Since HBB was launched in 2010, a 47% reduction in neonatal mortality and a 24% reduction in fresh stillbirths has been documented in areas that have implemented the program (AAP, n.d.). Because of the success of HBB, ECEB and ECSB were developed to help with the post-delivery care of the neonate. The same methodology of education is used with both ECEB and ECSB as in HBB.

SUMMARY

Although most depressed infants respond to drying, warming, positioning, suctioning, and tactile stimulation, every obstetric and neonatal unit should be adequately equipped and well prepared to

handle neonatal emergencies. To provide neonatal care effectively, nurses must understand the cardiorespiratory transition and must be able to identify factors that may interfere with successful transition, comprehend the principles of resuscitation, and intervene on the basis of assessment of respirations, heart rate, and color.

CASE STUDY

A 22-year-old Caucasian female is admitted to your hospital labor and delivery unit via the emergency squad. She was brought in with complaints of contractions and the feeling of *pressure* in her groin area. The mother states that she is approximately 25 weeks' gestation and her contractions began several hours ago. On exam, bulging intact membranes are found in the vagina and fetal heart tones are audible with a Category III tracing. She is prepped for an emergency cesarean section.

1. ***What equipment, personnel, and medications are needed to prepare for the resuscitation of the infant?***

   Increase the delivery room temperature to 76°F, preheat a radiant warmer in manual mode, and assure that a polyethylene bag and chemical thermal mattress are available for use. Assemble personal protective equipment and ensure that a pediatric or neonatal stethoscope is present. A bulb syringe should be present as well as a suction catheter with tubing connected to wall suction set at 100 mmHg. For intubation a properly functioning laryngoscope with an appropriate size blade, a 2.5 and 3.0 ET tube, a pulse oximeter and cardiac monitor should be at the bedside. An umbilical cord insertion tray with a 3.5 umbilical catheters should be present as well as 1:10,000 epinephrine 0.5 to 1.0 mL/kg drawn up in a 3 mL syringe for ET administrations and 0.1 to 0.3 mL/Kg drawn up in a 1 mL syringe for IV administration. Additional personnel will be required to assist with the resuscitation, with at least one that is capable of intubating and placing an umbilical line if needed.

   The baby is born by cesarean section; she appears to be 25 weeks' gestation and approximately 600 g and the obstetrician delays cord clamping for 30 seconds, holding the baby at the level of the introitus with a sterile towel covering the baby. The baby is handed to you blue, limp, and not breathing.

2. ***What are your initial steps?***

   Place on preheated radiant warmer in a polyethylene bag; place temperature probe on infant and switch to servo mode; place hat on baby's head; position head in a sniffing position; continue to stimulate; suction the infant's mouth, then nose; provide blow-by oxygen; place pulse oximeter on baby's right hand.

   Your evaluation after carrying out the initial steps of resuscitation shows that the infant remains apneic with a heart rate of 40 and a pulse oximeter reading of 50.

3. ***What do you do next?***

   Start bag/mask ventilation with oxygen between 30% and 40% concentrations at a rate of 40 to 60 bpm. Reevaluate the infant in 30 seconds.

   After 30 seconds of bag/mask ventilation, the infant remains apneic; her heart rate remains at 40 bpm, pulse oximeter reading 50.

4. ***What are your next steps?***

   Check to ensure that the chest is rising and, if not, take steps for correction per the NRP and continue bag/mask ventilation with oxygen at 100%; begin cardiac compressions at a ratio of 3 to 1. Prepare equipment for intubation.

   The baby is intubated orally with a 2.5 ET tube on the first attempt. There are no spontaneous respirations, and the heart rate improves to 60 bpm and pulse oximeter 60.

5. ***What are your next steps?***

   Discontinue compressions, secure the ET tube, and continue to bag with oxygen at a rate of 40 to 60 breaths/minute.

   The infant is pink, has no spontaneous respirations, and her heart rate continues to increase to 100 bpm and pulse oximeter reading is now 70.

6. ***What would you do next?***

   Continue to bag the infant via the ET tube, and move the infant from the delivery room to the newborn unit.

7. ***What would your initial steps of stabilization be upon the infant's admission to the unit?***

   Place in a neutral thermal environment with 80% humidity
   Obtain glucose
   Start an IV of $D_{10}W$ at 80 mL/kg/day
   Obtain a complete blood count with differential and platelets
   Obtain a blood culture
   Place infant on a ventilator: FiO_2—100%, P/P—20/5, IMV—40, IT—.3
   Obtain a blood gas
   Surfactant—4 mL/kg
   Ampicillin—100 mg/kg q12h
   Gentamicin—5 mg/kg q36h

EVIDENCE-BASED PRACTICE BOX

In recent years the use of 100% oxygen in neonatal resuscitation has been reevaluated to the point that the new AAP NRP advocates the starting of resuscitation for term infants in 21% oxygen and something greater than 21% but less than 100% for preterm infants. This change of philosophy in the use of oxygen is a result of multiple studies that show that there are no advantages of 100% oxygen over 21% and the hyperoxia effects of oxygen to a neonate can be detrimental in the long term.

One set of studies (Cnattingius et al., 1995; Naumberg, Bellocco, Cnattingius, Jonzon, & Ekbom, 2002) that has shown the negative effects of oxygen use in the immediate postpartum period for the neonate shows an increase in childhood lymphatic leukemia. Both studies showed that infants resuscitated with 100% oxygen with a face mask immediately postpartum had an increased risk of developing childhood lymphatic leukemia, and if they received oxygen for greater than 3 minutes by manual ventilation, the risks increased.

Randomized controlled clinical studies have shown that there are no advantages in starting resuscitation with 100% oxygen over 21% oxygen, and it actually takes longer for an infant to take its first breath or to cry. Meta-analyses by Davis, &

(*continued*)

EVIDENCE-BASED PRACTICE BOX (*continued*)

Dawson (2012) and Rabi Singhal, & Nettel-Aguirre (2011) show that neonates resuscitated with 21% oxygen had slightly lower mortality rates than those resuscitated with 100% oxygen. Animal studies have shown potentially harmful damage at the cellular level from oxygen.

Research continues on the effects of oxygen on the developing neonate, and as more evidence continues to emerge, there will be changes to how we resuscitate newborns.

References

Cnattingius, S., Zack, M. M., Ekbom, A., Gunnarskoq, J., Kreuger, A., Linet, M., & Adami, H. O. (1995, June 21). Prenatal and neonatal risk factor for childhood lymphatic leukemia. *Journal of the National Cancer Institute, 87*(12), 908–914. doi:10.1093/jnci/87.12.908

Davis, P. G., & Dawson, J. A. (2012). New concepts in neonatal resuscitation. *Current Opinion in Pediatrics, 24(2)*, 147–153. doi:10.1097/MOP.0b013e3283504e11

Naumberg, E., Bellocco, R., Cnattingius, S., Jonzon, A., & Ekbom, A. (2002). Supplementary oxygen and risk of childhood lymphatic leukemia. *Acta Pediactrica, 91*, 1328–1333. doi:10.1111/j.1651-2227.2002.tb02829.x

Rabi, Y., Singhal, N., & Nettel-Aguirre, A. (2011). Room air versus oxygen administration for resuscitation of preterm infants: The ROAR study. *Pediatrics, 128*, e374–e381. doi:10.1542/peds.2010.3130

ONLINE RESOURCES

American Academy of Pediatrics. (n.d.). Neonatal Resuscitation Program. Retrieved from http://www.aap.org/nrp

The S.T.A.B.L.E. (n.d.). *The S.T.A.B.L.E.® program*. Retrieved from https://stableprogram.org

University of Virginia Health System. (n.d.). *Perinatal continuing education program*. Retrieved from https://med.virginia.edu/cme/learning/pcep/

REFERENCES

American Academy of Pediatrics. (2017). Statement of endorsement: Delayed cord clamping after birth. *Pediatrics, 139*(6), e20170957. doi:10.1542/peds.2017-0957

American Academy of Pediatrics. (2018). Survive and thrive: Five year report. *Helping Babies Survive*. Retrieved from https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/helping-babies-survive/Pages/default.aspx

American College of Obstetrics and Gynecology. (2017). Committee opinion no. 684: Delayed cord clamping after birth. *Obstetrics and Gynecology, 129*(1), e5–e10. doi:10.1097/ACOG.0000000000001860

American Heart Association. (n.d.). *Guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Part 13: Neonatal resuscitation*. Retrieved from https://eccguidelines.heart.org/index.php/circulation/cpr-ecc-guidelines-2/part-13-neonatal-resuscitation/?strue=1&id=2

American Heart Association Emergency Cardiac Care Committee and Subcommittees. (1992). Guidelines for cardiopulmonary resuscitation and emergency cardiac care. VII. Neonatal resuscitation. *Journal of the American Medical Association, 268*, 2276–2281. doi:10.1001/jama.268.16.2276

Castrodale, V., & Rinehart, S. (2014). The golden hour: Improving stabilization of the very low birth weight infant. *Advances in Neonatal Care, 14*(1), 9–14. doi:10.1097/ANC.0b013e31828d0289

Dawson, J. A., Saraswat, A., Simionato, L., Thio, M., Kamlin, C. O., Owen, L. S., . . . Davis, P. G. (2013). Comparison of heart rate and oxygen saturation measurements from Masimo and Nellcor pulse oximeters in newly born term infants. *Acta Paediatrics, 102*(10), 955–960. doi:10.1111/apa.12329

Dunn, M. S., Kaempf, J., de Klerk, A., de Klerk, R., Reilly, M., Howard, D., . . . Soll, R. (2011). Randomized trial comparing 3 approaches to the initial respiratory management of preterm neonates. *Pediatrics, 128*(5), e1069–e1076. doi:10.1542/peds.2010-3848

Efrat, R., Kadari, A., & Katz, S. (1994). The LMA in pediatric anesthesia: Experience with 120 patients undergoing elective groin surgery. *Journal of Pediatric Surgery, 29*(2), 206–208. doi:10.1016/0022-3468(94)90319-0

Finer, N. N., Carlo, W. A., Walsh, M. C., Rich, W., Gantz, M. G., Laptook, A. R., . . . Higgins, R. D. (2010). Early CPAP versus surfactant in extremely preterm infants. *New England Journal of Medicine, 362*, 1970–1979. doi:10.1056/NEJMoa0911783

Flanders, S. A., & Strasen, J. H. (2014). Review of evidence about family presence during resuscitation. *Critical Care Nursing Clinics of Nursing America, 26*(4), 533–550. doi:10.1016/j.ccell.2014.08.010

Gandini, D., & Brimacombe, J. (2004). Manikin training for neonatal resuscitation with the laryngeal mask airway. *Pediatric Anesthesia, 14*(6), 493–494. doi:10.1111/j.1460-9592.2004.01247.x

Jones, B. L., Parker-Raley, J., Maxson, T., & Brown, C. (2011). Understanding health care professionals' views of family presence during pediatric resuscitation. *American Journal of Critical Care, 20*(3), 199–207. Retrieved from http://ajcc.aacnjournals.org/content/20/3/199.full

Kamlin, C. O., O'Donnell, C. P., Everest, N. J., Davis, P. G., & Morley, C. J. (2006). Accuracy of clinical assessment of infant heart rate in the delivery room. *Resuscitation, 71*, 319–321. doi:10.1016/j.resuscitation.2006.04.015

Katheria, A., Rich, W., & Finer, N. (2012). Electrocardiogram provides a continuous heart rate faster than oximetry during neonatal resuscitation. *Pediatrics, 130*, e1177–e1181. doi:10.1542/peds.2012-0784

Lambeth, T. M., Rojas, M. A., Holmes, A. P., & Dail, R. B. (2016). First golden hour of life: A quality improvement initiative. *Advances in Neonatal Care, 16*(4), 264–272. doi:10.1097/ANC.0000000000000306

Matterson, H. H., Szyld, D., Green, B. R., Howell, H. B., Pusic, M. V., Mally, P. V., & Bailey, S. M. (2018, February 16). Neonatal resuscitation experience curves: Simulation based mastery learning booster sessions and skill decay patterns among pediatric residents. *Journal of Perinatal Medicine, 46*(8), 934–941. doi:10.1515/jpm-2017-0330

Micaglio, M., Doglioni, N., Parotto, M., Zanardo, V., Ori, C., & Trevisanuto, D. (2006). Training for neonatal resuscitation with the laryngeal mask airway: A comparison of the LMA Pro-Seal and the LMA-Classic in an airway management manikin. *Pediatric Anesthesia, 16*(10), 1028–1031. doi:10.1111/j.1460-9592.2006.01921.x

Mizumoto, H., Tomotaki, S., Shibata, H., Ueda, K., Akashi, R., Uchio, H., & Hata, D. (2012). Electrocardiogram shows reliable heart rate much earlier than pulse oximetry during neonatal resuscitation. *Pediatric International, 54*, 205–207. doi:10.1111/j.1442-200X.2011.03506

Mosley, C. M., & Shaw, B. N. (2013). A longitudinal cohort study to investigate the retention of knowledge and skills following attendance

on the newborn life support course. *Archives of Diseases of Childhood, 98*(8), 582–586. doi:10.1136/archdischild-2012-303263

Oczkowski, S. J., Mazzetti, J., Cupido, C., & Fox-Robichaud, A. E.; for the Canadian Critical Care Society. (2015). Family presence during resuscitation: A Canadian Critical Care Society paper. *Canadian Respiratory Journal, 22*(4), 201–205. doi:10.1155/2015/532721

Perlman, J. M., Wyllie, J., Kattwinkel, J., Wyckoff, M. H., Aziz, K., Guinsburg, R., . . . Velaphi, S. (2015). Part 7: Neonatal resuscitation: 2015 International consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. *Circulation, 132*(Suppl. 1), S204–S241. doi:10.1161/CIR.0000000000000276

Surcouf, J. W., Chauvin, S. W., Ferry, J., Yang, T., & Barkemeyer, B. (2013). Enhancing residents' neonatal resuscitation competency through unannounced simulation-based training. *Medical Education Online, 18*. doi:10.3402/meo.v18i0.18726

Trevisanuto, D., Micaglio, M., Pitton, M., Magarotto, M., Piva, D., & Zanardo, V. (2004). Laryngeal mask airway: Is the management of neonates requiring positive pressure ventilation at birth changing? *Resuscitation, 62*, 151–157. doi:10.1016/j.resuscitation.2004.03.006

van Vonderen, J. J., Hooper, S. B., Kroese, J. K., Roest, A. A., Narayen, I. C., van Zwet, E. W., & te Pas, A. B. (2015). Pulse oximetry measures a lower heart rate at birth compared with electrocardiography. *Journal of Pediatrics, 166*, 49–53. doi:10.1016/j.peds.2014.09.015

Weiner, G. M. (Ed.). (2016). *Textbook of neonatal resuscitation* (7th ed.). Elk Grove, IL: American Academy of Pediatrics and American Heart Association.

Wyckoff, M. H., Aziz, K., Escobedo, M. B., Kapadia, V. S., Kattwinkel, J., Perlman, J. M., . . . Zaichkin, J. G. (2015). Part 13: Neonatal resuscitation: 2015 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care (Reprint). *Circulation, 132*(Suppl. 2), S543–S560. doi:10.1161/CIR.0000000000000267

Zanardo, V., Simbi, A. K., Savio, V., Micaglio, M., & Trevisanuto, D. (2004). Neonatal resuscitation by laryngeal mask airway after elective cesarean section. *Fetal Diagnosis and Therapy, 19*, 228–231. doi:10.1159/000076703

Zhu, X. Y., Lin, B. C., Zhang, Q. S., Ye, H. M., & Yu, R. J. (2011). A prospective evaluation of the efficacy of the laryngeal mask airway during neonatal resuscitation. *Resuscitation, 82*(11), 1405–1409. doi:10.1016/j.resuscitation.201106.010

CHAPTER 4

Assessment of the Newborn and Infant

Terri A. Cavaliere

INTRODUCTION

Assessment is a continuous process of evaluation throughout the course of routine care of the neonate and infant. However, periodically a more formalized, comprehensive examination must be undertaken to determine wellness or to evaluate a specific problem. The results of the comprehensive physical assessment serve as the database on which clinical judgments about diagnosis and treatment are based.

A comprehensive physical assessment is performed for various reasons. The assessment may be the initial examination at birth, assessment of extrauterine transition, determination of gestational age (GA), comprehensive assessment after transition, discharge examination, well-baby outpatient examination, or evaluation of an illness or injury. Although these assessments have many commonalities, each has a somewhat different purpose. The importance of a comprehensive physical assessment cannot be overstressed. While advances in technology have improved our ability to provide care to newborns, there is no substitute for hands-on assessment. This chapter discusses various aspects of a comprehensive physical assessment.

FIRST NEONATAL ASSESSMENT AND THE APGAR SCORE

The initial neonatal assessment occurs immediately after delivery with the assignment of Apgar scores. These scores were devised in 1952 by Virginia Apgar as a means of assessing the clinical status of infants immediately after delivery (Apgar, 1953). The Apgar score consists of five components—heart rate, respiratory effort, muscle tone, reflex irritability, and color—and each component is given a score of 0, 1, or 2; the scores are then added to obtain a total score (Table 4.1). It should be assigned at 1 and 5 minutes; however, if the total score is below 7 at 5 minutes, the assessment is repeated every 5 minutes for up to 20 minutes.

The Apgar score, once used to direct resuscitative efforts, has now become an acknowledged and rapid means of evaluating a neonate's clinical condition and/or the response to resuscitation (American Academy of Pediatrics [AAP] Committee on Fetus and Newborn & American College of Obstetricians and Gynecologists [ACOG] Committee on Obstetric Practice, 2015). It is important to recognize that elements of the Apgar score may be influenced by a variety of factors besides birth asphyxia, including, but not limited to, preterm birth, administration of drugs to the mother,

TABLE 4.1

APGAR SCORING SYSTEM

Component	Assigned Score		
	0	1	2
Heart rate (beats/minute)	Absent	<100 (slow)	100
Respiratory effort	None	Weak cry; hypoventilation	Good, strong cry
Muscle tone	Limp	Some flexion	Active motion
Reflex irritability	No response	Grimace	Cough or sneeze
Color	Blue or pale	Body pink; extremities blue	Completely pink

Source: Adapted from Goldsmith, J. P. (2015). Overview and initial management of delivery room resuscitation. In R. J. Martin, A. A. Fanaroff, & M. C. Walsh (Eds.), *Fanaroff & Martin's neonatal-perinatal medicine: Diseases of the fetus and infant* (10th ed., Vol. 1, pp. 460–470). Philadelphia, PA: Elsevier.

interobserver variability, and congenital anomalies. A low 1-minute Apgar score does not correlate with the newborn's future outcome. The 5-minute Apgar score, especially the change in the score between 1 and 5 minutes, reflects the effectiveness of resuscitation efforts. However, even a 5-minute score of 0 to 3, although possibly a result of hypoxia, is limited as an indicator of the severity of the problem and in and of itself correlates poorly with future neurologic outcome (Stanley, 1994; Weiner, Zaichkin, & Kattwinkel, 2016).

The Apgar score is not meant to be used to determine the need for resuscitation nor should it be used in isolation to predict morbidity or mortality for any particular neonate, but to convey information about the newborn's response to resuscitation (Goldsmith, 2015). Values of components of the Apgar score are affected by

resuscitation; therefore, the chart should reflect what measures, if any, are underway (Weiner et al., 2016).

An Apgar score assigned during resuscitation is not equivalent to a score assigned to a spontaneously breathing infant. No accepted standard exists for assigning an Apgar score during resuscitation after birth; many of the elements contributing to the score are affected by resuscitation. The creation of a score that accounts for resuscitative efforts has been proposed; however, the predictive reliability of such a tool has not been established (AAP Committee on Fetus and Newborn & ACOG Committee on Obstetric Practice, 2015).

In addition, appropriateness of the Apgar score to evaluate extremely premature infants has also been examined. The maturity of the infant influences certain elements of the Apgar score, such as reflex irritability, muscle tone, and respiratory effort; thus, it is likely that healthy premature infants, without indications of asphyxia, may have lower Apgar scores than term infants (AAP Committee on Fetus and Newborn & ACOG Committee on Obstetric Practice, 2015; Als & Butler, 2011).

OTHER CONSIDERATIONS FOR THE INITIAL NEONATAL ASSESSMENT

Before the infant leaves the delivery area, a brief physical examination should be performed. Considerations for this assessment include inspection for birth injuries and major congenital anomalies and evaluation of pulmonary and cardiovascular adjustment to extrauterine life. Evaluation of early transition to extrauterine life includes observation of color for adequacy of perfusion and oxygenation; assessment of respiratory effort; auscultation of breath sounds and heart sounds; and inspection of the amount, color, and consistency of secretions. Tone activity and appropriateness of state should also be noted at this time. A cursory inspection of all external areas should be performed before the infant leaves the delivery area, including a general evaluation of the external genitalia and, in males, palpation for testes in the scrotum. The entire examination should be performed under a radiant heat source to prevent significant heat loss from the infant.

Evaluation of Transition

Adaptation to both intrapartum and neonatal events is reflected in the transition from a fetal to an extrauterine environment. These events result in sympathetic activity that affects the infant's color, respiration, heart rate, behavioral state, gastrointestinal function, and temperature (Gardner & Hernandez, 2016). It is important to remember that the physiologic and biochemical changes peculiar to the period of transition to extrauterine life affect the physical findings of early examinations. The examination performed during transition is described separately because characteristics that are normal during transition may be abnormal if they appear at other times.

As the neonate's circulation converts from the fetal route, there may be a period in which pulmonary vascular resistance remains greater than systemic vascular resistance, resulting in a right to left shunt across the ductus arteriosus. Higher preductal oxygen saturation causes the neonate's face and upper body to appear pink while the lower body and legs appear pale or blue; this creates a visible demarcation across the chest. As the fetal circulation successfully converts to the neonatal pathway, this transitional differential cyanosis disappears (Levy & D'Harlingue, 2013). Acrocyanosis is common during this period. To evaluate babies with deeper skin pigmentation, the nurse should observe the color of the mucous membranes. When the neonate is stimulated, the skin may appear blushed or bright red; this change in color is called erythema neonatorum, or generalized hyperemia, which develops a few hours after birth. It generally resolves within several minutes to an hour and rarely appears with the same intensity (Gomella, 2013). Erythema neonatorum is not synonymous with erythema toxicum neonatorum.

The neonatal heart rate may range from 160 to 180 beats/minute (bpm) in the first 15 minutes of life; it slowly falls to a baseline rate of 100 to 120 bpm by 30 minutes of life. The heart rate is labile, and brief periods of asymptomatic, irregular heart rates are not pathologic. Murmurs are common, because the ductus arteriosus may still be patent. Respirations are also irregular during the first 15 minutes, with rates ranging from 60 to 100 breaths/minute. Grunting, flaring, retractions, and brief periods of apnea may also be seen in the neonate. Crackles may be present on auscultation (Gardner & Hernandez, 2016).

Despite the changes in the heart and respiratory rates during the initial 15 to 30 minutes of life, healthy term infants are awake and alert. They may rest quietly, cry periodically, startle spontaneously, and breastfeed during this period. Full-term babies often show flexed posture with good muscle tone; preterm newborns, in comparison, have less flexion and tone (Cavaliere & Sansoucie, 2014). Temperature is decreased, and gastrointestinal activity includes the establishment of bowel sounds and the production of saliva. This first period of reactivity may be prolonged in infants who have experienced difficult labor and delivery, in sick term infants, and in well premature infants (Gardner & Hernandez, 2016).

After the first period of reactivity, the infant is relatively unresponsive or sleeping, and the heart rate drops to a baseline of 100 to 120 bpm. This interval, which lasts approximately 60 to 100 minutes, is followed by a second period of reactivity, which lasts anywhere from 10 minutes to several hours. During this time the infant may show rapid color changes, intermittent tachypnea and tachycardia, and changes in tone. A healthy infant may have periods during which the respiratory rate is considerably higher than 60 breaths/minute; however, the infant does not appear distressed and can slow this rate enough to nipple feed successfully. Meconium often is passed during this period (Cavaliere, 2016; Gardner & Hernandez, 2016). The chart in Figure 4.1 summarizes some of the physical changes seen during the transition period.

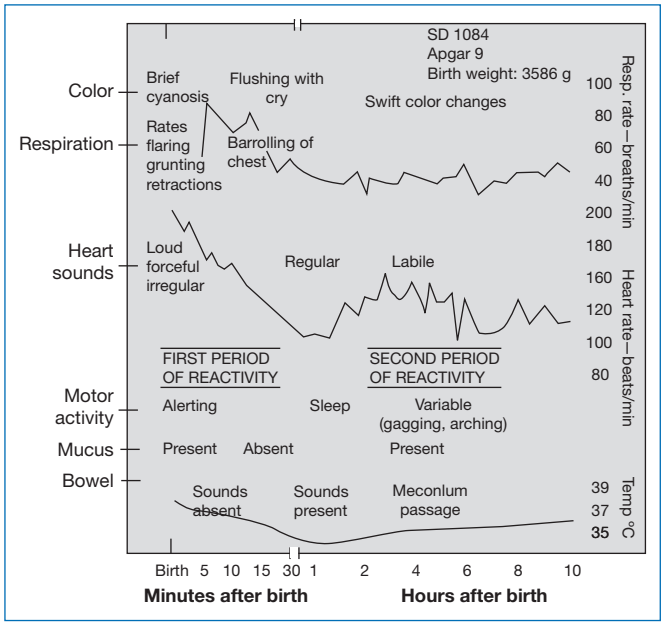


FIGURE 4.1 Normal transition period.

Source: Based on Desmond, M. M., Rudolph, A. J., & Phitaksphraiwan, P. (1966). The transitional care nursery. A mechanism for preventive medicine in the newborn. *Pediatric Clinics of North America, 13*(3), 651–668. doi:10.1016/S0031-3955(16)31875-2

Newborn Examination

The comprehensive newborn examination generally is performed within the first 12 to 18 hours of life, after transition has been completed successfully. The examination should be initiated when the infant is quiet and should progress from assessments that are least likely to bother the infant to those that are most irritating. An examination sequence based on the infant's state is outlined in Table 4.2.

Discharge Examination

The purpose of the discharge examination is to assess the infant's ability to be cared for outside the controlled environment of the hospital. The focus of the assessment depends primarily on how long the infant has been hospitalized and for what reasons. The needs of a healthy, full-term infant being discharged home with the mother are different from those of a growing, preterm infant who has been hospitalized for weeks or months and who has significant

TABLE 4.2

EXAMINATION SEQUENCE BASED ON INFANT'S STATE

Assessment Technique	Required State	Arousing Maneuver	Equipment
Observe general appearance			
Observe color			
Observe resting posture	Quiet		
Observe spontaneous activity	Active		
Count respirations	Quiet		Clock
Count heartbeats	Quiet		Clock
Inspect facies at rest	Quiet		
Auscultate heart sounds	Quiet		Stethoscope
Auscultate breath sounds	Quiet		Stethoscope
Measure blood pressure	Quiet		Blood pressure cuff
Inspect head and neck region			
Stimulate response to sound	Quiet		Calibrated noise maker
Inspect trunk anteriorly			
Palpate abdomen, cardiac impulse	Quiet		
Feel pulses			
Examine genitalia			Lubricant for rectal examination
Inspect trunk posteriorly			
Inspect arms and hands			
Inspect legs and feet			
Assess passive tone			
Assess active tone	Active	X	

(*continued*)

TABLE 4.2

EXAMINATION SEQUENCE BASED ON INFANT'S STATE (*continued*)

Assessment Technique	Required State	Arousing Maneuver	Equipment
Elicit primitive reflexes	Active	X	
Assess muscle strength	Active	X	
Assess GA			
Test range in major joints		X	
Manipulate hips		X	
Measure temperature			Thermometer
Examine ears			Otoscope
Determine pupil response			Bright light
Examine fundi	Quiet	X	
Elicit tendon reflexes		X	Percussion hammer
Stimulate response to pain		X	
Weigh infant	Quiet	X	Scales, growth chart
Measure head circumference			Tape measure, growth chart
Measure chest and abdominal circumferences		X	Tape measure
Measure length			Tape measure, growth chart
Transilluminate head		X	High-intensity light
Percuss abdomen	Quiet		
Percuss lungs	Quiet		

GA, gestational age.

Source: Data from Fletcher, M. A. (1998). *Physical diagnosis in neonatology.* Philadelphia, PA: Lippincott-Raven.

sequelae. Evaluating the caretaker's capability to care for and observe changes in the infant is an important aspect of the discharge assessment and follow-up plan. Anticipatory guidance regarding feedings, sleeping position and environment, skin care, safety practices, and recognition of signs and symptoms of illness should be provided at this time.

Outpatient Examination

The focus of the first outpatient examination is the infant's adaptation to the home environment. This examination includes assessment of any issues highlighted at discharge. Some factors to be considered in the infant are temperature stability, ability and success at feeding and elimination, sleep patterns, normal color, drying of the umbilical cord, reassessment of hip stability, and normal state and behavior. Any areas that may have been relatively inaccessible during earlier examinations should be included, such as the eyes, ear canals, and eardrums (Fletcher, 1998).

The birth history, including the birth weight, GA, and any problems, should be reviewed. As part of the complete physical examination, height, weight, and head circumference should be plotted and developmental progress observed. The results of newborn metabolic screening and the infant's immunization status

should be reviewed. For sick infants, general assessment assists in the establishment of priorities. For example, if a child is experiencing pronounced respiratory problems, assessment of this area is a priority. Anticipatory guidance issues include nutrition, elimination, sleep patterns, development and behavior, social and family relationships, and injury prevention. A more detailed description of health maintenance for high-risk infants during the first year of life is presented later in this chapter.

Environment

The routine neonatal assessment should take place in a quiet, warm environment. The room should be lighted well enough for appropriate observation, but the light should not be so strong that the infant is deterred from opening the eyes. Prevention of heat loss is critical to the infant's comfort and to the maintenance of thermal neutrality and glucose homeostasis. Most healthy term infants can tolerate being undressed in a reasonably warm room for the 5 to 10 minutes required to perform the physical assessment. If the environment is cool or drafty or if the infant is sick or preterm, an external heat source should be provided, such as a radiant warmer or heat lamps. If heat lamps are used, the infant's eyes should be shielded to prevent adverse effects from prolonged exposure of the infant's eyes to the bright light of the lamps. The examiner should warm the hands and examination equipment before beginning the assessment. This practice not only prevents heat loss but also avoids upsetting an otherwise quiet and cooperative infant.

The examination should be conducted in a quiet environment with a calm infant. A placid infant provides the best opportunity for gathering meaningful data. Extraneous environmental noise hampers auscultation and assessment of bodily sounds and may overwhelm a sick or immature infant, causing changes in state and cardiovascular status (Honeyfield, 2019). Handling the infant gently and speaking in a soothing voice may allow the examiner to complete most of the assessment without distressing the infant. Disturbing components of the examination, such as deep palpation of the abdomen and assessment of the hips, should be performed last.

Having one or both parents present during the routine neonatal assessment offers the opportunity to assess their competence in care giving and to educate them about the unique physical traits, behavior, and coping skills of their infant. The examiner may also use this time to build rapport and trust with the parents, to listen to their concerns, and to offer pertinent information. Some issues may require privacy for discussion; therefore, confidentiality should be considered when conversing with parents in the presence of others.

COMPONENTS OF A COMPREHENSIVE HISTORY

The neonatal history is very similar to that for an older child or adult, including information about the past medical history, the current condition, and the family. For a newly delivered infant, the initial neonatal assessment probably will be conducted before the nurse speaks to the parents. Basic information about the pregnancy and delivery should be available in the maternal records, but a complete history lays the foundation for the comprehensive newborn examination and should be elicited directly from the parents. Without a complete history, the examiner may lack adequate information to formulate an accurate impression.

The components of a complete history are the identifying data; chief complaint; interim neonatal history or history of presenting problem or illness; antepartum history; obstetric history; intrapartum history; and the maternal medical, family medical, and social histories (Table 4.3). After data collected from the complete history and physical assessment are organized and all expected and unexpected findings have been reviewed, areas of concern are identified and prioritized for further evaluation and attention. This forms the framework for the clinical diagnosis and plan of care.

Interviewing the Parents

The interview with the parents is a vital component of the health assessment of a newborn or an infant. This interview offers the nurse an excellent opportunity to develop a therapeutic partnership with the parents in the care of their baby. Ideally, the interview is conducted in a quiet, comfortable setting; if it takes place at the bedside in a busy intensive care unit, the parents may be distracted and overwhelmed by the sounds and sights customary to this environment. If the ideal setting is not possible, the nurse can provide a focal point of warmth and attention by using a conversational tone of voice, maintaining eye contact, and concentrating fully on the parents. However, this can be done only with a discipline that dispels both personal and professional distractions.

It is important that nurses introduce themselves and clearly state their names and roles in the baby's care. Nurses should make sure they understand the parents' names and should pronounce them correctly. They should ask the baby's name and use it often during the conversation. During this session, the purposes of the health interview and physical assessment should be clarified. Cooperation and sharing are more likely if the parents understand that the questions lead to better care for their infant.

The use of silence and listening, as well as allowing ample time for response to questions, is crucial to reassuring parents that what they say is worthwhile. Also, the parents can easily be shown that the interview is important and will not be rushed. Nurses should fix their attention on the parents and listen and should not interrupt unless necessary. They also should avoid asking the next questions before listening to the complete answer to the current question. They should indicate that they understand the responses and should request clarification if necessary. Nurses should take care to avoid overly technical language, medical jargon, and the tendency to inundate the parents with information. They should attempt to verify that the parents understand what has happened and what they have been told and that they seem to be coping. Nurses should always discuss and explain what the parents can expect to happen next; they should also bring up methods of keeping in touch, pertinent telephone numbers, and the visitation policy, if appropriate.

It is often difficult to approach parents about sensitive matters, such as drug or alcohol use or concerns about the death of their infant. The following is a list of suggestions that may assist in the discussion of sensitive issues as offered by Ball, Dains, Flynn, Solomon, and Stewart (2015):

- Respect the individual's privacy
- Avoid discussing sensitive topics where the conversation might be overheard
- Begin the discussion with open-ended questions and ask the least threatening questions first
- Not be patronizing, but use language that is straightforward and understandable
- Take a direct and firm approach
- Avoid apologizing for asking a question (the nurse is doing nothing wrong)
- Avoid lecturing (the nurse is not there to pass judgment)

TABLE 4.3

COMPONENTS OF A COMPREHENSIVE NEONATAL HISTORY

Component	Data Required
Identifying data	Infant's name; parents' names; parents' telephone numbers (home and work); infant's date of birth, gender, and race; and source of referral (obstetric or pediatric provider) if any.
Chief complaint	Statement of initial known status (age, gender, birth and current weights, and GA by dates and examination) and problems infant might have; for a newborn or well-baby examination, the statement simply reflects the current health status (e.g., "Full-term male infant, now 1 week of age, for well-baby follow-up").
Interim history/ history of newborn	Chronologic record of newborn's history from time of delivery to present or, if older infant, presenting problem chronologic narrative of chief complaint. Narrative should answer questions related to where (location), what (quality, factors that aggravate or relieve symptoms), when (onset, duration, frequency), and how much (intensity, severity).
Antepartum history	Historical data about the pregnancy, including maternal age, gravidity, parity, last menstrual period, and estimated date of delivery. Date and GA at which prenatal care began, provider of care, and number of visits should be recorded here. Mother's health during pregnancy, infections, medications taken, use of illicit drugs or alcohol, abnormal bleeding, and results of prenatal screening tests should also be included.
Obstetric history	Significant history regarding previous pregnancies; neonatal problems or subsequent major medical problems of previous children and current age and health status of living children should be noted.
Intrapartum history	Duration of labor, whether it was spontaneous or induced, duration of rupture of membranes, type of delivery, complications; infant's birth weight, presentation at delivery, and Apgar scores; resuscitative measures if required and response to those measures.
Past medical history	Significant maternal history of chronic health problems or diseases treated in the past or during the pregnancy, including surgical procedures and hospitalizations before or during the pregnancy. For older infants, also obtain information about infant's history, including feeding, development, illness, and immunizations.
Family medical history	Significant family medical history of chronic disorders, disabilities, known hereditary diseases, or consanguinity.
Social history	Parents' marital status, paternal involvement, parents' occupations, and educational level; sources of financial support, housing accommodations, and insurance status must be noted, as well as any support agencies involved. Family unit should be defined and religious and cultural affiliations noted, along with number of individuals living in the home. Plans for child care should be elicited, as well as any current family stressors (e.g., moving, death in the family).

GA, gestational age.

- Understand that defensive behavior might be the individual's way of coping
- Proceed slowly and take care not to demean the individual's behavior
- Offer feedback to ensure that the individual agrees that your interpretation is appropriate
- Provide an opportunity for the individual to ask relevant questions

It is vital that, in communicating with parents from diverse cultures, nurses appreciate and respect differences in communication patterns and in childbearing and health practices. Knowledge of cultural variations in family and health practices assists nurses in developing sensitivity to differences; however, the family must be observed carefully for cues to family practices and relationships with children and one another.

Incorporation of a family history tool such as *My Family Health Portrait Tool* (www.hhs.gov/programs/prevention-and-wellness/family-health-history) developed by the U.S. Department of Health and Human Services will give at least a three-generation history that may reveal genetic conditions. Some families will already have completed this information online. The tool takes very little time to complete and can be used in conjunction with the standard history questions.

Physical Assessment Techniques

The techniques used for physical assessment are inspection, palpation, percussion, and auscultation. Learning these skills requires patience and practice, and the inability of the newborn to provide verbal cues presents an additional challenge. With experience, the practitioner learns to process a multitude of observations while assessing individual systems and then to use these data to form a clinical impression and plan of care.

Inspection. Inspection is the simple yet intricate use of the auditory and visual senses to evaluate an infant's state, color, respiratory effort, posture, and activity, as well as the shape and symmetry of

various body regions. It is a crucial skill in the physical assessment of neonates, but it is also a difficult one to master. The sense of smell may be used to note unusual odors. The impression obtained from methodical observation establishes priorities for the remainder of the systematic assessment. In the physical examination, thoughtful observation, rather than simple looking, is the most efficient means of detecting changes. Inspection should be used throughout the physical assessment and should continue as long as the infant remains in the nurse's care.

Auscultation. Auscultation is the process of listening for sounds made by the body. The bell of the stethoscope is used for low-pitched sounds (e.g., cardiovascular sounds) and the diaphragm for higher pitched sounds (e.g., lung and bowel sounds). The stethoscope should be placed lightly but firmly against the wall of the body part being assessed. A calm infant and quiet environment facilitate auscultation. Practice in recognizing normal body sounds is required before abnormal sounds can be identified accurately.

Palpation. With palpation, the examiner uses the sense of touch to determine hydration, texture, tension, pulsation, vibration, amplitude, and tenderness, as well as the depth, size, shape, and location of deep structures. The touch used for palpation must be gentle and is performed with the flats of the finger pads rather than the fingertips (Fletcher, 1998; Honeyfield, 2019). To gather the most accurate information, the infant should be calm at the onset of the abdominal examination. Relaxing the abdominal musculature by flexing the infant's knees and hips with one hand facilitates palpation of the liver and spleen. Gentle pressure must be emphasized during palpation of sensitive organs (e.g., liver, spleen, and skin) that are at greater risk for injury and bleeding in neonates, particularly preterm infants, or those that have hepatomegaly. Warming of the examiner's hands, use of a pacifier, and progression from superficial to deep palpation help maintain the infant's comfort throughout most of the examination. Tender areas should always be palpated last.

Percussion. Percussion is the use of tapping to produce sound waves that may be assessed according to intensity, pitch, duration, and quality (Table 4.4). Percussion may be direct or indirect. For direct percussion, the examiner directly strikes the body part to be assessed with the tip of the middle right finger. For indirect percussion, the examiner places the middle finger of the nondominant hand against the skin of the body part to be assessed and strikes the distal joint with the tip of the middle finger of the dominant hand. The wrist must make a snapping motion, creating a brisk thump with the tip of the right middle finger against the left middle finger's distal joint. Vibrations are transmitted from the bones of the finger joint touching the infant's body to the underlying tissue (Figure 4.2). Although percussion is rarely used in neonatal assessment, it may be a useful technique for examining the older infant or child.

Assessment of Size and Growth

Well-being in the fetal and neonatal periods is reflected by a normal growth pattern. Fetal and neonatal growth rates are predictable and can be measured by various methods. To determine if an individual infant's growth is adequate, an appropriate standard must be used with which the child's measurements can be compared. The growth curves used must match the patient as closely as possible in gender, race, GA, genetic potential, and environmental factors, such as altitude. A discussion of the techniques used to estimate and assess fetal growth is beyond the scope of this chapter and can be found elsewhere in this text. Two methods of evaluating adequacy of growth in the newborn are the GA assessment and the clinical assessment of nutritional status. One tool that may be used to assess nutritional status in the clinical setting is the clinical assessment of nutritional status score (CANSCORE) developed by

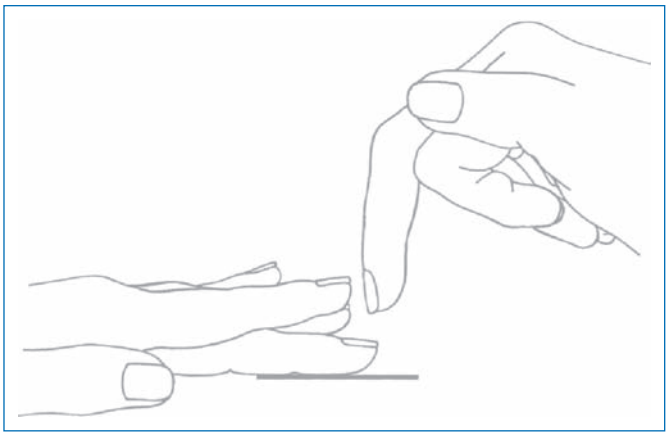


FIGURE 4.2 Percussion technique. Note the position of the fingers.

Source: From Engel, J. (2006). *Pocket guide to pediatric assessment* (5th ed.). St. Louis, MO: Mosby.

TABLE 4.4

PERCUSSION SOUNDS

Type of Sound	Intensity	Pitch	Duration	Quality	Common Locations
Tympany	Loud	High	Moderate	Drumlike	Gastric bubble; air-filled intestine (simulate by tapping puffed out cheeks)
Resonance	Moderate to loud	Low	Long	Hollow	Lungs
Hyperresonance	Very loud	Very low	Long	Booming	Lungs with trapped air; lungs of a young child
Dullness	Soft to moderate	High	Moderate	Thudlike	Liver, fluid-filled space (e.g., stomach)
Flatness	Soft	High	Short	Flat	Muscle

Source: Data from Engel, J. (2006). *Pocket guide to pediatric assessment* (5th ed.). St. Louis, MO: Mosby.

McLean and Usher (1970). See the text that follows for more information about the CANSCORE.

Assessment of GA

A determination of GA is part of the physical examination of every newborn. Classification of newborns by GA enables the healthcare provider to determine the neonatal mortality risk (Figure 4.3) and to identify possible disorders (Figure 4.4) and initiate intervention or screening (Gardner & Hernandez, 2016). Figure 4.5 shows the classification of newborns by intrauterine growth and GA. Table 4.5 presents terms used in GA assessment and in determining the adequacy of in utero growth.

As was previously mentioned, morbidity and mortality can be predicted from the GA assessment (see Figures 4.3 and 4.4). Neonates with the lowest risk of problems associated with morbidity and mortality are term infants who developmentally are appropriate for gestational age (AGA). Risks associated with categories of GA and intrauterine growth restriction are shown in Table 4.6.

After birth, GA is determined by the evaluation of physical, neurologic, and neuromuscular characteristics. A number of methods have been developed to assess GA in newborns. The New Ballard score (NBS) is a widely used assessment tool (Figure 4.6). It includes six neurologic and six physical criteria and permits assessment of extremely premature infants. Despite its advantages over the other scoring systems, the NBS is accurate only to within 2 weeks and tends toward overestimating the GA of extremely premature neonates (Lissauer, 2015). Performing the examination as soon as possible in the first 12 hours of life enhances its accuracy.

Although GA assessment is discussed separately, the components of the assessment should be performed as part of the infant's general physical examination. Table 4.7 presents the essentials of the NBS; each component is scored as shown in Figure 4.6. The total score is calculated, and the resulting GA is plotted on a graph (see Figure 4.5).

Clinical Assessment of Nutritional Status

GA assessment does not identify all infants with intrauterine malnutrition. Although the terms *small for gestational age* (SGA) and *intrauterine growth retardation/restriction* (IUGR) are related, they are not synonymous. IUGR represents a reduction in the expected fetal growth pattern, whereas SGA refers to an infant whose birth weight is less than population norms. Not all IUGR infants are SGA, and not all SGA infants are IUGR (Calkins & Devaskar, 2015; Trotter, 2019).

Many but not all infants who are either SGA or IUGR are malnourished in utero. However, malnutrition can occur in neonates of any birth weight. Because malnutrition alters body composition and can prevent adequate brain growth, it is important to identify infants who have been affected in utero. These infants may be at risk for problems associated with aberrant growth (Calkins & Devaskar, 2015).

McLean and Usher (1970) initially described physical findings that are suggestive of weight loss or poor nutrition. These physical characteristics form the basis of the CANSCORE that may still be used in the clinical evaluation of nutritional status in the

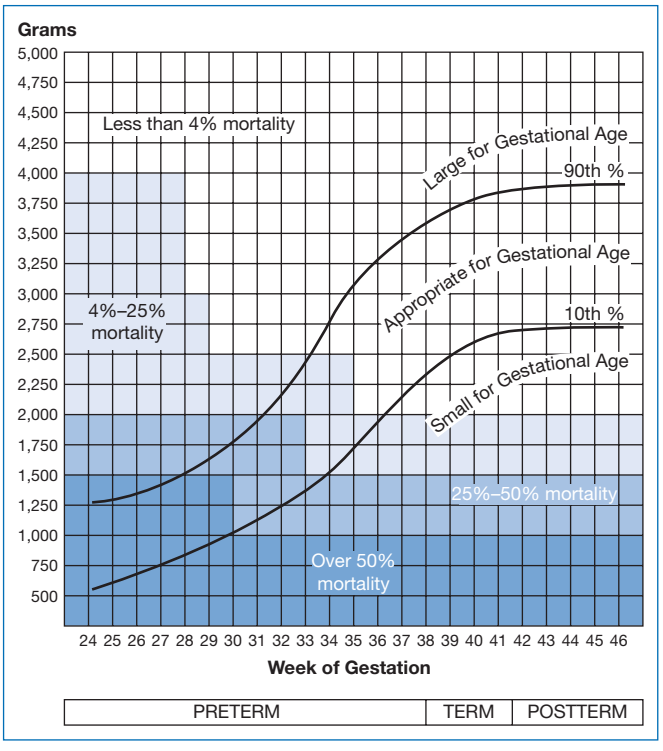


FIGURE 4.3 University of Colorado Medical Center classification of newborns by birth weight and gestational age and by neonatal mortality risk.

Source: From Battaglia, F. C., & Lubchenco, L. O. (1967). A practical classification of newborn infants by weight and gestational age. *Journal of Pediatrics, 71*, 159–163. doi:10.1016/S0022-3476(67)80066-0

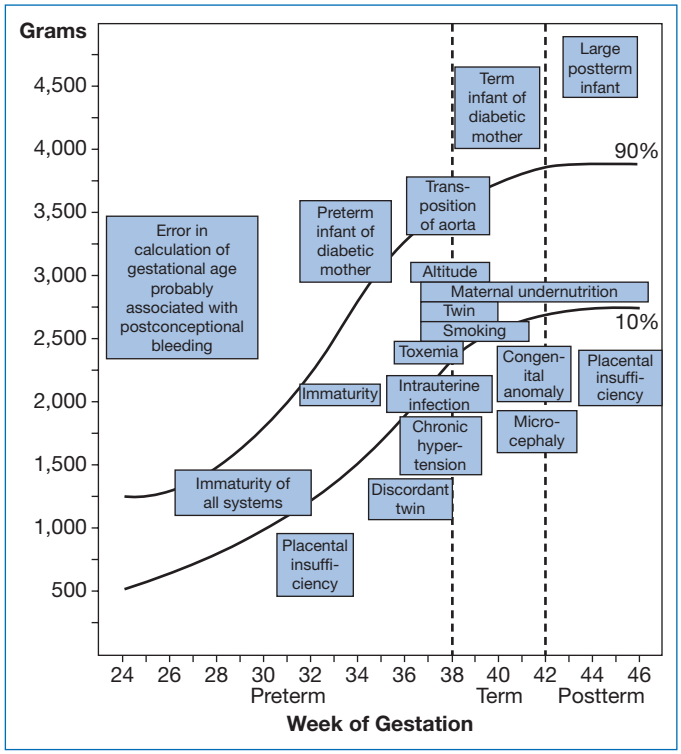
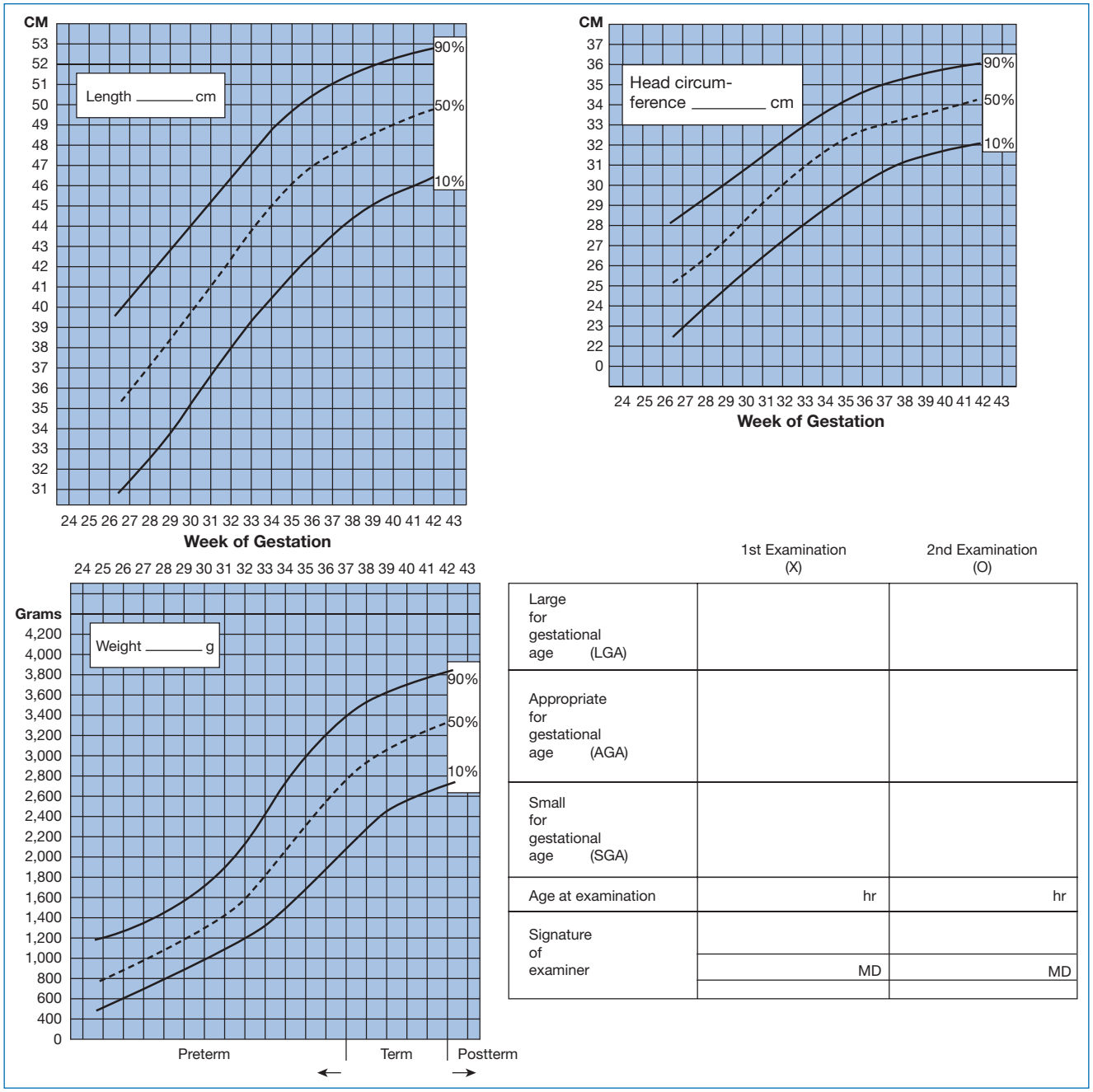


FIGURE 4.4 Deviations of intrauterine growth: Neonatal morbidity by birth weight and gestational age.

Source: Modified from Lubchenco, L. O. (1967). *The high risk infant.* Philadelphia, PA: Saunders.



	1st Examination (X)	2nd Examination (O)
Large for gestational age (LGA)		
Appropriate for gestational age (AGA)		
Small for gestational age (SGA)		
Age at examination	hr	hr
Signature of examiner	MD	MD

FIGURE 4.5 Estimating gestational age: Newborn classification based on maturity and intrauterine growth.

Sources: Modified from Battaglia, F. C., & Lubchenco, L. O. (1967). A practical classification of newborn infants by weight and gestational age. *Journal of Pediatrics, 71*, 159–163. doi:10.1016/S0022-3476(67)80066-0; Lubchenco, L., Hansman, C., & Boyd, E. (1966). Intrauterine growth in length and head circumference as estimated from live births at gestational ages from 26 to 42 weeks. *Pediatrics, 37*, 403–408. Retrieved from https://pediatrics.aappublications.org/content/37/3/403

clinical setting (Singhal, Agal, & Kamath, 2012). In addition to the CANSCORE, other tools that may be useful in assessing nutritional status are the ponderal index (PI) and the body mass index (BMI; Ezenwa & Ezeaka, 2018).

Measurement Techniques

For most infants the parameters of weight, length, and occipito-frontal circumference (OFC) are adequate for the basic physical assessment. These measurements are compared against standard growth curves. If the infant has any abnormalities in the size of a body component or if the infant shows disproportionate growth, the involved areas should be measured and compared with established norms (Fletcher, 1998).

Weight and Length. The infant should be weighed while unclothed and quiet. Weight can be falsely increased by several factors, including clothing and infant motion. The weight of the average full-term that is AGA is 3.5 kg, with a range of 2,700 to 4,000 g (Burton-Mota, 2014; Tappero, 2019). Birth weights are affected by genetics and geographic location. For instance, African American, Hawaiian, and Asian neonates weigh less than

TABLE 4.5

TERMS AND ABBREVIATIONS USED IN ASSESSMENT OF GA AND ADEQUACY OF INTRAUTERINE GROWTH

Term and Abbreviation	Description
Low birth weight	Infant weighing <2,500 g[a]
Very low birth weight	Infant weighing <1,500 g[a]
Extremely low birth weight	Infant weighing <1,000 g[a]
AGA	Parameter (weight) within the 10th–90th percentile for GA
LGA	Parameter above the 90th percentile for GA
SGA	Parameter below the 10th percentile for GA
IUGR	Slowing of intrauterine growth documented by ultrasound; a neonate may be IUGR without being SGA
Symmetric IUGR	Measurements for weight, length, and head circumference all within the same growth curve even if neonate is AGA, LGA, or SGA
Asymmetric IUGR	Measurements for weight, length, and head circumference in different growth curves
Term gestation	Neonate born between 37 and 42 weeks gestation
Preterm gestation	Neonate delivered before completion of week 37 of gestation
Postterm gestation	Neonate delivered after completion of week 42 of gestation

[a] Regardless of length of gestation.

AGA, appropriate for gestational age; IUGR, intrauterine growth restriction; LGA, large for gestational age; SGA, small for gestational age.

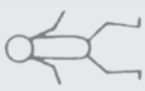
TABLE 4.6

RISKS ASSOCIATED WITH GESTATIONAL AGE AND INTRAUTERINE GROWTH RESTRICTION

Category	Risks
SGA, LGA, IUGR	Perinatal and long-term problems
Preterm SGA	Problems associated with immaturity of body systems and placental insufficiency
Preterm	Problems associated with immaturity of body systems
Postterm	Problems associated with placental insufficiency
Term LGA	Risks are greatest in perinatal period, but long-term problems can develop

IUGR, intrauterine growth retardation/restriction; LGA, large for gestational age; SGA, small for gestational age.

Neuromuscular Maturity

	–1	0	1	2	3	4	5
Posture							
Square Window (wrist)	 >90°	 90°	 60°	 45°	 30°	0°	
Arm Recoil		 180°	 140°–180°	 110° 140°	 90°–110°	 <90°	
Popliteal Angle	 180°	 160°	 140°	 120°	 100°	 90°	 <90°
Scarf Sign							
Heel to Ear							

Physical Maturity

Skin	sticky friable transparent	gelatinous red, translucent	smooth pink, visible veins	superficial peeling and/ or rash few veins	cracking pale areas rare veins	parchment deep cracking no vessels	leathery cracked wrinkled
Lanugo	none	sparse	abundant	thinning	bald areas	mostly bald	
Plantar Surface	heel-toe 40–50 mm: –1 <40 mm: –2	>50 mm no crease	faint red marks	anterior transverse crease only	creases ant. 2/3	creases over entire sole	
Breast	imperceptible	barely perceptible	flat areola no bud	stippled areola 1–2 mm bud	raised areola 3–4 mm bud	full areola 5–10 mm bud	
Eye/Ear	lids fused loosely: –1 tightly: –2	lids open pinna flat stays folded	sl. curved pinna; soft; slow recoil	well-curved pinna; soft but ready recoil	formed and firm instant recoil	thick cartilage ear stiff	
Genitals (male)	scrotum flat smooth	scrotum empty faint rugae	testes in upper canal rare rugae	testes descending few rugae	testes down good rugae	testes pendulous deep rugae	
Genitals (female)	clitoris prominent labia flat	prominent clitoris small labia minora	prominent clitoris enlarging minora	majora and minora equally prominent	majora large minora small	majora cover clitoris and minora	

Maturity Rating

score	weeks
–10	20
–5	22
0	24
5	26
10	28
15	30
20	32
25	34
30	36
35	38
40	40
45	42
50	44

FIGURE 4.6 Maturational assessment of GA: New Ballard scoring system.

Source: From Ballard, J. L., Khoury, J. C., Wedig, K., Wang, L., Eilers-Walsman, B. L., & Lipp, R. (1991). New Ballard score, expanded to include extremely premature infants. *Journal of Pediatrics, 119*, 417–423. doi:10.1016/S0022-3476(05)82056-6

TABLE 4.7

NEW BALLARD SCORING SYSTEM

Component	Assessment Technique	Effect of Maturity	Comments
Neuromuscular Maturity			
Posture	Observe infant while baby is unrestrained and supine; note amount of flexion and extension of extremities	Extensor tone is replaced by flexor tone in a cephalocaudal progression	Knees may be hyperextended in a frank breech delivery
Square window	Flex wrist; measure minimum angle formed by ventral surface of forearm and palm	Angle decreases; at term no space exists between palm and forearm	Response depends on muscle tone and intrauterine position
Arm recoil	Place infant in supine position with head in midline; flex elbow and hold forearm against arm for 5 seconds; fully extend elbow, then release; note time required for infant to resume flexed position	Angle decreases and recoil becomes more rapid	
Popliteal angle	Flex hips, placing thighs on abdomen; keeping hips on surface of bed, extend knee as far as possible until resistance is met; estimate popliteal angle	Popliteal angle decreases	Amount of extension can be beyond point where resistance is first met; this assessment also is affected by intrauterine position and hip dislocation
Scarf sign	With head in midline, pull hand across chest to encircle neck; note position of elbow relative to midline	Increased resistance to crossing the midline	Reflects muscle tone; response is altered by obesity, hydrops, or fractured clavicle
Heel to ear	Keep infant supine with pelvis on mattress; press feet as far as possible toward head, allowing knees to be positioned beside abdomen; estimate angle created by arc from back of heel to mattress	Angle decreases; hip flexion decreases toward term	Reflects muscle tone
Physical Maturity			
Skin	Observe translucency of skin over abdominal wall	Skin becomes thicker and ultimately dry and peeling; pigmentation increases	Skin becomes drier hours after birth; phototherapy or sunlight enhances pigmentation
Lanugo	Assess for presence and length of hair over back	Lanugo emerges at 19–20 weeks and is most prominent at 27–28 weeks; then gradually disappears, first from the lower back and then from at least half of the back	The degree of pigmentation and quantity of hair are related to race, nutritional status
Plantar surface	Measure length of foot; determine presence or absence of true deep creases (not merely wrinkles)	Early in gestation, foot length correlates with fetal growth; creases develop from toes to heel, and absence of creases correlates with immaturity	Plantar creases also reflect intrauterine fetal activity; accelerated creasing is seen with oligohydramnios; diminished creasing suggests lack of activity in a mature fetus
Breast	Estimate diameter of breast bud; assess color and stippling of areola	Definition and stippling of areola and pigmentation are evident near term; bud size increases because of maternal hormones and fat accumulation	With intrauterine growth restriction, breast tissue may be diminished, but development of areola proceeds regardless of malnutrition

(*continued*)

TABLE 4.7

NEW BALLARD SCORING SYSTEM (*continued*)

Component	Assessment Technique	Effect of Maturity	Comments
Ear cartilage	Fold top of auricle; observe speed of recoil	Cartilage becomes stiff, and auricle thickens	Compression in utero and absence or dysfunction of auricular muscles diminishes firmness
Eyelid opening	Without attempting to separate eyelids, evaluate degree of fusion	Opening begins at 22 weeks; lids are completely unfused by 28 weeks	Fused eyelids should not be considered a sign of nonviability; lids may be fused at term with anophthalmia
External Genitalia			
Male	Palpate scrotum to assess degree of descent of testes; observe rugae and suspension (cryptorchidism)	At 27–28 weeks, testes begin to descend into scrotum; rugae formation of scrotum begins at about 28 weeks; by term, rugae are well defined, and scrotum is pendulous	Rugae are decreased with scrotal edema; testes may be absent
Female	Assess size of labia minora and labia majora	Labia minora increase in size before labia majora; at term labia majora cover labia minora completely	Size of labia majora depends on amount of body fat; with malnutrition, size may be diminished; edema may increase size of labia majora

Sources: Data from Gardner, S. L., & Hernandez, J. A. (2016). Initial nursery care. In S. L. Gardner, B. S. Carter, M. I. Enzman-Hines, & J. A. Hernandez (Eds.), *Merenstein & Gardner's handbook of neonatal intensive care* (8th ed., pp. 71–104). St. Louis, MO: Elsevier; Lissauer, T. (2015). Physical examination of the newborn. In R. J. Martin, A. A. Fanaroff, & M. C. Walsh (Eds.), *Fanaroff & Martin's neonatal-perinatal medicine: Diseases of the fetus and infant* (10th ed., pp. 391–406). St. Louis, MO: Mosby.

Caucasian infants (Tappero, 2019) and populations that live in high altitudes have babies that are normally smaller than cohorts born at sea level. It is helpful to use growth graphs that are specific for populations and locations if they are available.

The crown-to-heel length can be obtained using a measurement board or a standard tape measure. With the infant supine and legs extended, the nurse draws a line on the bed at the baby's head and another at the heels and then measures the distance between these two points (Figure 4.7). The average full-term newborn is 50 cm long with a range of 48 to 53 cm (Tappero, 2019). Other measurement techniques are described in the appropriate sections.

Physical Examination of the Neonate

The following sections describe the newborn examination beyond the transition period.

Vital Signs. Once transition is complete, the neonate has a respiratory rate between 40 and 60 breaths/minute, and the rate may be irregular. Respirations are easy and unlabored; breath sounds should be clear on auscultation. The heart rate varies from 100 to 160 bpm, depending on the infant's state and GA (Vargo, 2019). Premature neonates have a higher baseline heart rate. The resting heart rate is the most representative for any baby.

Normal blood pressure ranges depend on GA and chronologic age and the methods used. Blood pressure in premature babies is proportional to size; therefore, normal values are lower than for term babies (Hegyi et al., 1994). Figures 4.8 and 4.9 and Tables 4.8 through 4.10 show normal blood pressure values over various time frames and GAs.

Temperature is determined by axillary measurement; acceptable values range from 35.5°C to 37.5°C (Gardner & Hernandez, 2016).

Cardiovascular Values. The heart is assessed for rate, rhythm, character of heart sounds, and presence of murmurs. During infancy the position of the heart changes and the point of maximal impulse (PMI) shifts (Fletcher, 1998). In the first few days of life the PMI is located at the fourth intercostal space at or to the left of the midclavicular line. Auscultation should be performed at the second and fourth intercostal spaces, cardiac apex, and axilla (Vargo, 2019). Murmurs are commonly heard before the ductus arteriosus closes completely. However, murmurs that are persistent may not be normal and require evaluation. Brief asymptomatic irregularities in rate and rhythm are not uncommon, especially in the preterm baby. The most common benign dysrhythmias are sinus bradycardia or tachycardia and premature atrial or ventricular contractions (Vargo, 2019). An ECG or heart monitor is needed to properly identify the abnormality. Exact identification of the abnormality cannot be made solely by auscultation.

A precordial impulse may be visible along the left sternal border during the first 6 hours (Fletcher, 1998; Vargo, 2019). In premature neonates, because of their thin skin and absence of subcutaneous fat, the precordial impulse may be visible for a longer period. Pulses are palpated for rate, strength, and synchrony.

Figure 4.10 shows the location of pulses in the neonate (Vargo, 2019). Radial or brachial pulses are compared for timing and intensity, and the same is then done for bilateral femoral pulses. Finally, the preductal and postductal pulses are examined.

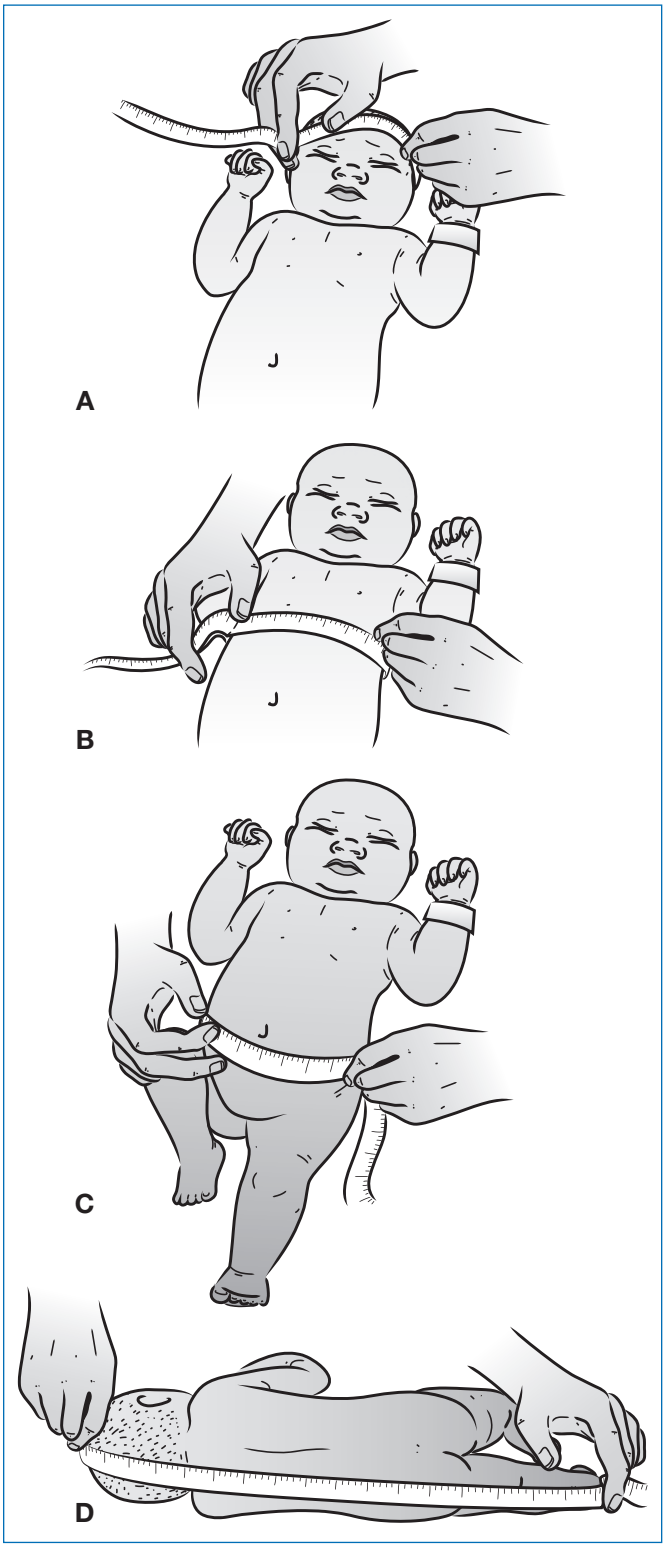


FIGURE 4.7 Newborn measurements. (A) Circumference of head, (B) circumference of chest, (C) circumference of abdomen, (D) length, crown to rump. (Total length includes the length of the legs.) If the measurements are taken before the infant's first bath, the nurse must wear gloves.

Source: Modified from Marjorie Pyle, RNC, Lifecircle, Costa Mesa, CA.

The adequacy of the infant's perfusion is determined by checking the capillary refill. This is assessed by depressing the skin over the abdomen or on an extremity until the area blanches. The capillary refill time is the number of seconds that elapse until the color returns to the area. This should be less than 3 seconds.

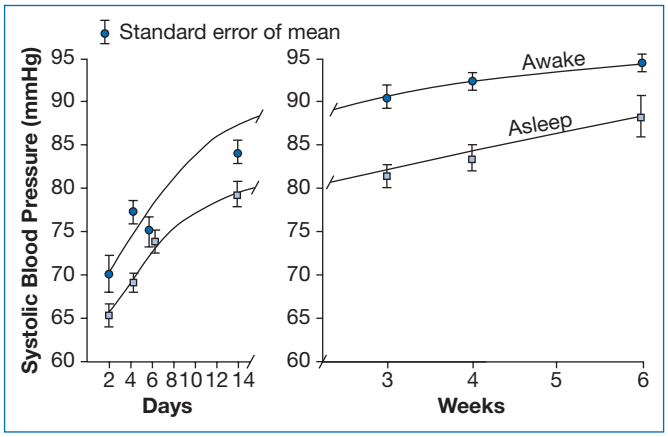


FIGURE 4.8 Increase in systolic blood pressure between ages 2 days and 6 weeks in infants awake and asleep (values obtained by cuff measurement).

Source: Modified from Earley, A., Fayers, P., Ng, S., Shinebourne, E. A., & de Sweit, M. (1980). Blood pressure in the first six weeks of life. *Archives of Disease in Childhood,* 55, 755–757. doi:10.1136/adc.55.10.755

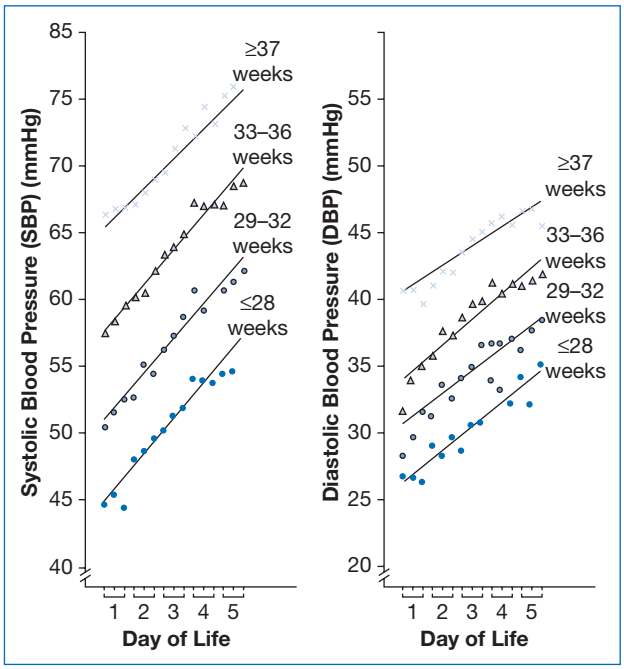


FIGURE 4.9 Systolic and diastolic blood pressures plotted for the first 5 days of life, with each day subdivided into 8-hour periods. Infants are categorized by gestational age into four groups: 28 weeks or younger ($n = 33$), 29 to 32 weeks ($n = 73$), 33 to 36 weeks ($n = 100$), and 37 weeks or older ($n = 110$).

Source: Modified from Zubrow, A. B., Hulman, S., Kushner, H., & Falkner, B. (1995). Determinants of blood pressure in infants admitted to neonatal intensive care units: A prospective multicenter study. Philadelphia Neonatal Blood Pressure Study Group. *Journal of Perinatology, 15,* 470.

General Appearance. The infant's general appearance is indicative of nutritional status, maturity, and overall well-being. Term neonates normally are well formed and rounded and have stores of subcutaneous fat. They assume the fetal position at rest. Premature babies may display less flexion than those born at term. Movement should be spontaneous and tremulous. Neonates range in mood from quiet to alert; they are consolable when crying. A normal cry is strong and sustained.

Skin. The skin is assessed for maturity, consistency, and color. Discolored areas, variations, or abnormalities are noted for size and

TABLE 4.8

BLOOD PRESSURE VALUES ACCORDING TO SITE AND AGE

	Blood Pressure (mmHg)		
Site and Age	Systolic	Diastolic	Mean
Calf			
<36 hours old	61.9 ± 7	39.6 ± 5.3	47.6 ± 6
>36 hours old	66.8 ± 10.1[a]	42.5 ± 7.3[a]	51.5 ± 9[a]
Total	63.6 ± 8.6	40.6 ± 6.3	49 ± 7.5

Notes: Values were obtained by blood pressure cuff measurement in 219 healthy term infants, 140 less than 36 hours old and 79 over 36 hours old. Values are given as means ± standard deviation.

[a] Significantly different from values in infants less than 36 hours old ($p < .05$).

TABLE 4.9

BLOOD PRESSURE RANGES IN DIFFERENT WEIGHT GROUPS OF PREMATURE NEWBORNS

	Blood Pressure (mmHg)	
Birth Weight (g)	Systolic	Diastolic
501–750 ($n = 18$)	50–62	26–36
751–1,000 ($n = 39$)	48–59	23–36
1,001–1,250 ($n = 30$)	49–61	26–35
1,251–1,500 ($n = 45$)	46–56	23–33
1,501–1,750 ($n = 51$)	46–58	23–33
1,751–2,000 ($n = 61$)	48–61	24–35

Notes: Measurements were obtained by blood pressure cuff or umbilical artery transducer in the first 3 to 6 hours of life.

Source: From Hegyi, T., Carbone, M. T., Anwar, M., Ostfeld, B., Hiatt, M., Koons, A., … Paneth, N. (1994). Blood pressure ranges in premature infants. I. The first hours of life. *Journal of Pediatrics, 124*, 627–633. doi:10.1016/S0022-3476(05)83146-4

location. The skin of a full-term newborn contains subcutaneous fat that provides insulation against heat loss. It is smooth, pink, and wrinkle free. Premature infants lack subcutaneous fat; their skin is thinner than that of term babies and has visible blood vessels over the chest and abdomen. Extremely immature babies often have a gelatinous appearance with transparent skin. They commonly have a red, ruddy color caused by underdevelopment of the stratum corneum. Subcutaneous fat also is lacking in neonates

TABLE 4.10

OSCILLOMETRIC MEASUREMENTS: MEAN ARTERIAL BLOOD PRESSURE

	Mean Arterial Pressure ± Standard Deviation		
Birth Weight (g)	Day 3	Day 17	Day 31
501–750	38 ± 8	44 ± 8	46 ± 11
751–1,000	43 ± 8	45 ± 7	47 ± 9
1,001–1,250	43 ± 8	46 ± 9	48 ± 8
1,251–1,500	45 ± 8	47 ± 8	47 ± 9

Source: With permission from Fanaroff, A. A., & Wright, E. (1990). Profiles of mean arterial blood pressure (MAP) for infants weighing 500–1500 grams. *Pediatric Research, 27*, 205A.

who are IUGR. This group of babies may have loose skin folds, particularly around the knees.

Vernix is the greasy yellow or white substance found on fetal skin, particularly in the axillary, nuchal, and inguinal folds. Composed of sebaceous gland secretions, lanugo, and desquamated epithelial cells, it protects against fluid loss and bacterial invasion (Sherman, 2015; Witt, 2019). Vernix is most abundant during the third trimester and decreases in amount as the fetus approaches 40 weeks.

Lanugo is fine, downy hair that first appears on the fetus at 19 to 20 weeks gestation and becomes most prominent at 27 to 28 weeks. It begins to disappear from the lower back and usually is not present at term.

Head. The head is inspected for shape, symmetry, bruises, and lesions. Neonates delivered by cesarean section generally have a rounded head. Infants born vaginally in vertex position can have overriding sutures; this results in an irregularly shaped head that persists only for a few days in full-term neonates but may be evident for several weeks in premature babies (Lissauer, 2015). The head circumference is measured in the occipitofrontal plane and is the largest diameter around the head. It is obtained with the tape measure placed snugly above the ears, the eyebrow ridges, and the occiput of the head. The average OFC in a full-term neonate is 35 cm, with a normal range of 31 to 38 cm (Johnson, 2019). The major bones of the head, as well as sutures and fontanelles, are shown in Figure 4.11.

The head should be palpated to assess the firmness of bone and the size and configuration of fontanelles and sutures and also to detect swelling, masses, or bony defects. The amount of overlap of sutures may vary, depending on the extent of molding. Normally the sutures should move freely when gentle pressure is applied to the bones on opposite sides of the suture lines (Furdon & Clark, 2003). Directly after birth, it may be difficult to determine if the sutures are fused or merely overlapping. Reevaluation when molding and overlap have resolved may yield more reliable information about the presence of craniosynostosis (Johnson, 2019).

The anterior fontanelle is 2 to 3 cm wide, 3 to 4 cm long, and diamond shaped (see Figure 4.11). It should be flat and soft; tense, bulging fontanelles may be reflective of intracranial pressure, while a sunken fontanelle can signify dehydration (Johnson, 2019). The

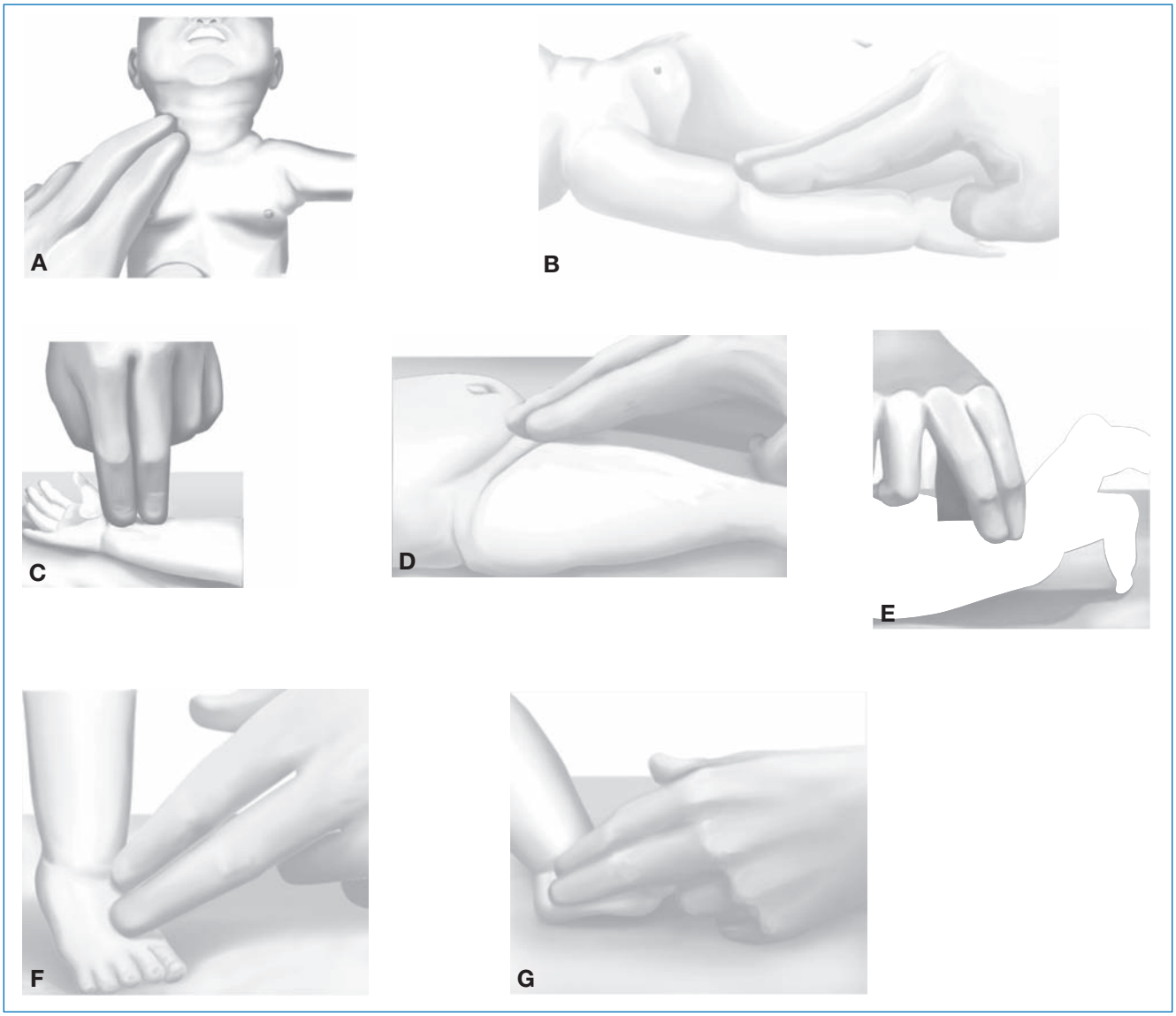


FIGURE 4.10 Palpation of arterial pulses. (A) Carotid, (B) brachial, (C) radial, (D) femoral, (E) popliteal, (F) dorsalis pedis, and (G) posterior tibial.

posterior fontanelle is 1 to 2 cm wide and triangular. It may be difficult to palpate the fontanelles directly after birth because of cranial molding. Tension in the fontanelle should be assessed with the infant both recumbent and upright. Serial measurements of the width of the anterior fontanelle are more helpful than a single measurement because of wide variations in size and differences in measurement techniques (Fletcher, 1998).

Hair is evaluated for color, length, continuity, texture, quantity, position and number of hair whorls, and hairlines. Term newborns have fine hair with identifiable individual strands. Hair may appear disheveled for the first several weeks to months (Fletcher, 1998). In premature neonates the hair is more widely dispersed and is described as "fuzzy." Normally, hair color is fairly uniform, although some neonates have a blend of light and dark hair (Furdon & Clark, 2003). Sporadic patches of white hair may be a familial trait and is a benign finding, but a white forelock and other pigmentation defects in the eyes or skin may be associated with deafness or mental retardation (Fletcher, 1998; Waardenburg, 1951). The anterior hairline varies, with normal growth of pigmented hair onto the forehead of hirsute babies. The posterior hairline ends at the neck crease. Usually one off-center hair whorl is present in the parietal region (Furdon & Clark, 2003).

Face and Neck. The face should be inspected for shape, symmetry, and the presence of bruising or dysmorphic features. The overall facial configuration should be evaluated; the features should be proportional and symmetric. Unusual facial features may be familial or pathognomonic of a malformation syndrome. Gag, sucking, and rooting reflexes should be evaluated.

The newborn has a relatively short neck that should be palpated or observed for symmetry, appearance of the skin, range of motion, masses, and fistulous openings. The neck should be symmetric with the head, demonstrating full range of motion (Carley & Duderstadt, 2019). In utero positioning can cause asymmetry of the neck. Redundant skin or webbing may be evident (Walker, 2018). The clavicles can be palpated at this time; they should be intact and without crepitus or swelling.

Ears. The ears are evaluated and compared for shape, configuration, position, amount of cartilage, and signs of trauma. The position

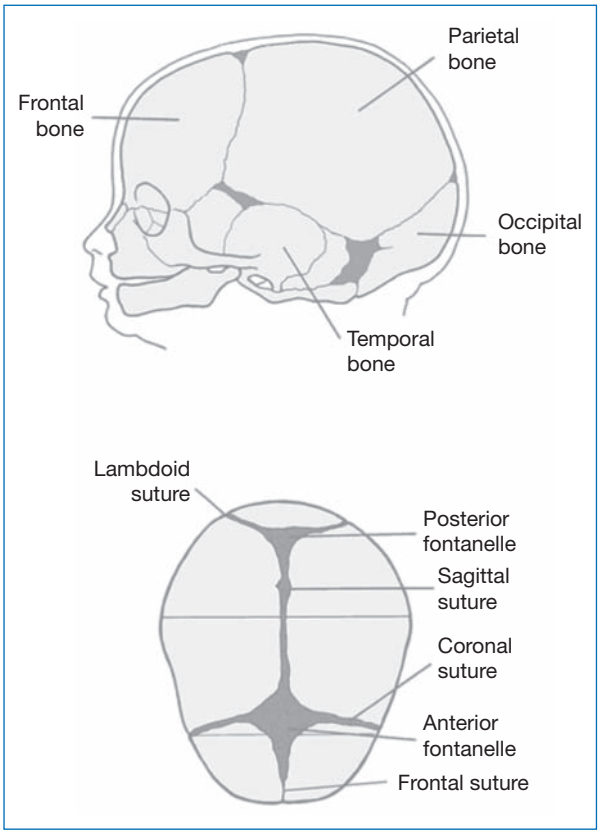


FIGURE 4.11 Major bones of the head in the newborn with sutures and fontanelles.

Source: Modified from Fletcher, M. A. (1998). *Physical diagnosis in neonatology.* Philadelphia, PA: Lippincott-Raven.

of the ears at term should be similar bilaterally; approximately 30% of the pinna should lie above a line from the inner and outer canthi of the eye toward the occiput. The rotation of the ears should also be assessed; the long axis of the pinna should lie approximately 15° posterior to the true vertical axis of the head (Fletcher, 1998; Figure 4.12). Abnormalities of the external ear may be associated with syndromes, but often they represent minor structural variations and may be within the normal range (Johnson, 2019).

The presence and patency of the auditory canal can be documented by inspection. Otoscopic examination is not usually part of the examination in the newborn period because the ear canals are filled with vernix, amniotic debris, and blood. This condition clears in approximately 60% of term infants by 1 week of age but may persist for weeks. Less debris is seen in preterm babies, whose canals may clear more quickly.

Because infants frequently remain hospitalized beyond the neonatal period and because evaluation of the middle ear is part of a health maintenance examination, it is appropriate to include otoscopic examination in this section. The otoscope is used differently in young infants than in adults. In a neonate the ear lobe is pulled toward the chin, and the speculum is directed toward the face. The ear canals of preterm babies are prone to collapse because they are more pliable. Positive pressure applied through the pneumatic otoscope prevents the cartilaginous ear canal from obscuring the view (Fletcher, 1998). The neonatal tympanic membrane is thicker, grayer, and more vascular than that of an adult or older child (Figure 4.13).

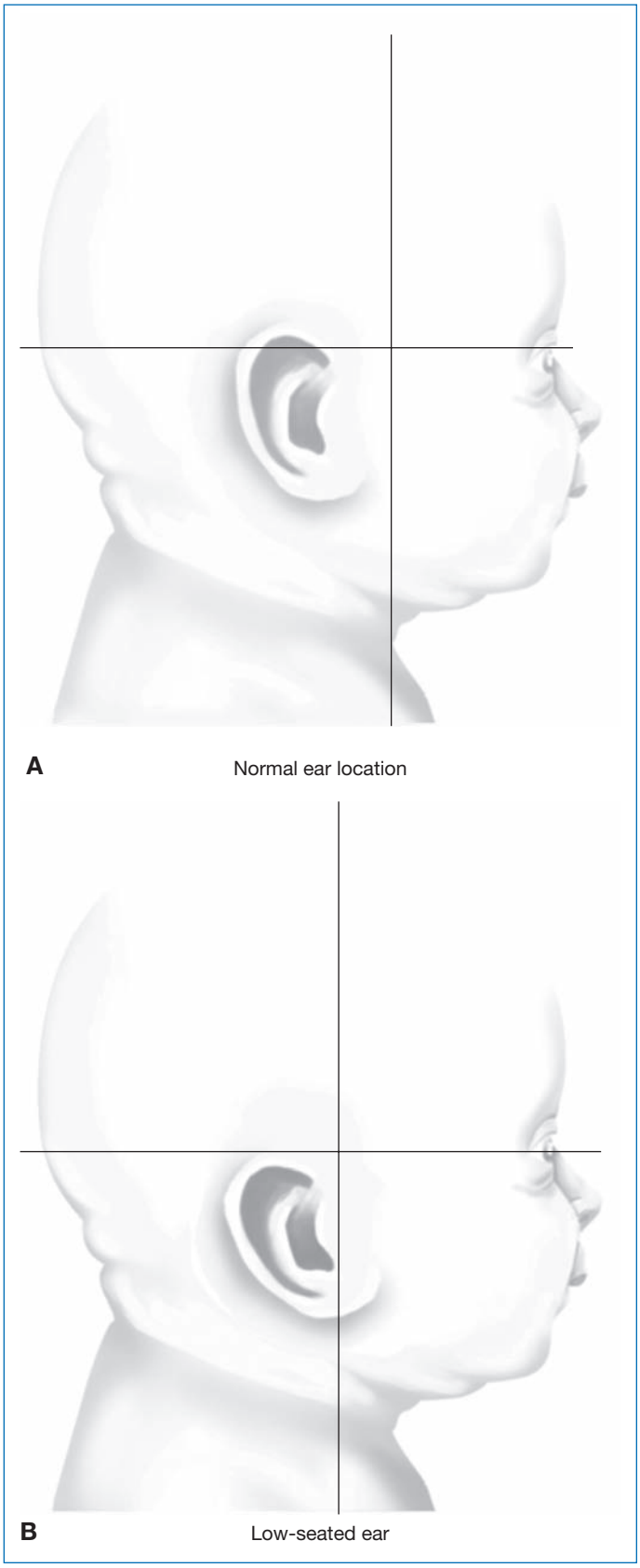


FIGURE 4.12 Normal (left) and low-seated (right) ear positions.

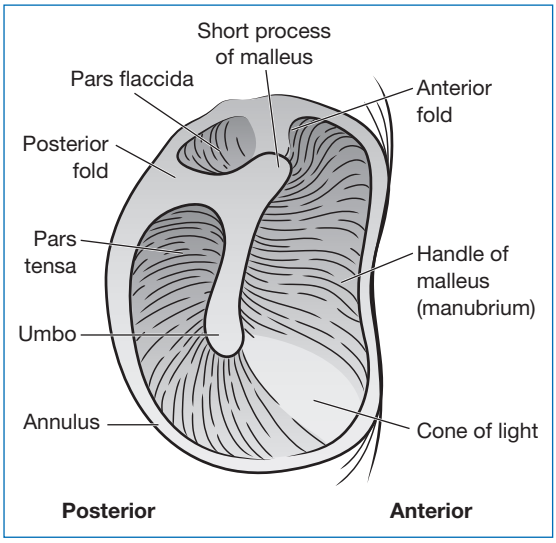


FIGURE 4.13 Normal landmarks of the right tympanic membrane as seen through an otoscope.

Source: Modified from Lewis, S. M., Bucher L., Heitkemper, M. M., Harding, M. M, Kwong, J., & Roberts, D. (2017). *Medical-surgical nursing: Assessment and management of clinical problems* (10th ed.). St. Louis, MO: Elsevier.

Universal hearing screening programs are mandated by law in all 50 states (Centers for Disease Control and Prevention, n.d.).

Eyes. The eyes should show spontaneous range of motion and conjugate movements. The lids should be symmetric in both horizontal and vertical placement, and the lashes should be directed outward in an orderly fashion. The eyes should be clear and should have an evenly colored iris, which may be dark gray, blue, or brown, depending on race. Pigmentation should be similar between the two eyes. Permanent eye color is not established for several months, but darker races may show permanent pigmentation in the first week of life. The surface of the conjunctiva should be smooth. During the first few days of life, the cornea may appear slightly hazy as a result of corneal edema, but thereafter the cornea should be clear and shiny. The sclerae normally are white, but a bluish coloration may be noted in premature and other small infants because their sclerae are thinner (Fletcher, 1998; Orge & Grigorian, 2015).

An ophthalmoscope is used to assess the pupillary and red reflexes. The light should be directed on the pupils from a distance of approximately 6 inches. The pupils should be round and equal in diameter and should constrict equally in response to light (pupils equal and reactive to light, or PERL; Johnson, 2019). The beam of light illuminating the retina causes the red reflex. The retina (fundus) appears as a yellowish-white/gray or red background, depending on the amount of melanin in the pigment epithelium. The pigment varies with the complexion of the baby; in dark-skinned infants, the reflex will be pale or cloudy (Honeyfield, 2019; Lissauer, 2015).

Nose. The nose should be evaluated for shape and symmetry, patency of nares, skin lesions, or signs of trauma. The nasal mucosa should be pink and slightly moist; secretions should be thin, clear, and usually scanty (Fletcher, 1998). The nose should be midline. Immediately after birth the nose may be misshapen as a result of compression in utero, but this should correct spontaneously in a few days (Fletcher, 1998). Obstructions and deformities may denote anatomic malformations or congenital syndromes. The patency of the nares can be demonstrated by alternate occlusion of each naris using gentle pressure (Fletcher, 1998). Nasal flaring may be indicative of respiratory distress, but in an otherwise healthy newborn it does not indicate respiratory distress when it appears as the only symptom (Gardner & Hernandez, 2016).

Mouth. The mouth is inspected for size, shape, color, and presence of abnormal structures and masses. It should be evaluated both at rest and while the infant is crying. The speed of response and intensity of neonatal reflexes, such as rooting, gagging, and sucking, are also assessed. The mouth is a midline structure and symmetric in shape and movement. The mouth, chin, and tongue should be in proportion, with the lips fully formed (Johnson, 2019; Heaberlin, 2019).

The mucous membranes should be pink and moist, and oral secretions should be thin and clear. Excessive secretions or drooling suggests inability to swallow or esophageal or pharyngeal obstruction. Both the hard and soft palates should be inspected and palpated to rule out clefts. A high-arched palate may be seen in malformation syndromes, but it generally is insignificant if it appears as an isolated characteristic (Lissauer, 2015).

The tongue should be smooth on all surfaces; the lingual frenulum may be short but not so short as to restrict tongue movement. Limitation of movement would be obvious on crying, when the tip of the tongue would form an inverted *V* (Fletcher, 1998; Johnson, 2019).

Thorax. The chest is evaluated for size, symmetry, musculature, bony structure, number and location of nipples, and ease of respiration. It should be symmetric in shape and movements. Because the anteroposterior diameter is approximately equal to the transverse diameter, the chest appears round. The chest circumference of a term infant should be about 2 cm smaller than the head circumference (Fraser, 2019). At all GAs, the chest measurement normally is smaller than the OFC (Duderstadt, 2019).

Occasional mild subcostal retractions may be seen in healthy newborns because of decreased compliance of the ribs. A paradoxical breathing pattern is typical of newborns, especially during sleep. On inspiration the chest wall is drawn in and the abdomen protrudes; the reverse occurs on expiration (Fletcher, 1998). However, in neonates with respiratory distress, this may be indicative of inadequate lung compliance and deficiency of lung volume (Fraser, 2019).

The amount of breast tissue depends on the GA and birth weight, whereas areolar development reflects only GA. Two nipples should be present in equal alignment. The internipple distance varies by GA and chest circumference, but the distance from the outer edge of one areola to the outer edge of the other should be less than 25% of the circumference of the chest (Fraser, 2019). Widely spaced nipples are associated with a variety of congenital syndromes (Fraser, 2019).

Newborn breast tissue may hypertrophy as a result of the influence of maternal hormones. A milky substance (witch's milk) may appear toward the end of the first week of life, and this discharge may persist for a few weeks to several months (Fraser, 2019).

Abdomen. The abdomen is inspected for contour and size, symmetry, character of skin, and umbilical cord location and anatomy. Palpation yields information about muscle mass and tone of the abdominal wall, location and size of viscera, tenderness, and masses (Goodwin, 2019). Bowel sounds are detected on auscultation; they are relatively quiet in newborns until feedings are established. Compared with term babies, preterm neonates have less active bowel sounds. Evaluating changes in bowel sounds from the infant's baseline is more clinically useful than an isolated assessment (Fletcher, 1998).

The normal abdomen in an infant is round and soft and protrudes slightly. The umbilical cord should be bluish white, shiny, and moist and should have two arteries and one vein. To facilitate palpation, the knees and legs should be flexed toward the hips,

which allow the abdominal muscles to relax. The edge of the liver can be palpated 1 to 2 cm below the right costal margin at the midclavicular line; this edge should be smooth, firm, and well defined (Goodwin, 2019). The tip of the spleen can be felt below the left costal margin in newborn infants. The size of the spleen depends on variables such as circulating blood volume, day of life, method of delivery, and type of therapy, which must be considered when interpreting the significance of mild enlargement (Fletcher, 1998).

The kidneys are located in the flanks. The lower pole of both kidneys should be palpable because of the reduced tone of neonatal abdominal muscles (Vogt & Dell, 2015). The kidneys should be smooth and firm to the touch. Enlarged kidneys are somewhat easy to detect, but normal-size neonatal kidneys may be somewhat more difficult to find. The presence of renal tissue is confirmed when voiding has occurred (Cavaliere, 2019).

Anogenital Area. The anogenital area should be examined with the infant supine. GA affects the appearance of the external genitalia. Maturational changes are described in Figure 4.6 and Table 4.7. The genitalia should be readily identifiable as male or female.

- *Males:* The normal length of the penis at term is 3.5 cm (±0.7 cm; Fletcher, 1998). Gentle traction is applied on the foreskin to visualize the urethral meatus; the opening should be at the central tip of the glans. Physiologic phimosis, a nonretractable foreskin, normally is seen in newborns. The opening in the prepuce should be large enough to allow urination. The urine stream should be forceful and straight. The inguinal area and scrotum should be palpated for masses, swelling, and the presence of testes. The testes should be firm, smooth, and comparatively equal in size. Testicular descent begins at approximately 27 weeks' gestation. At term both testes should be in the scrotum, which should be fully rugated. The scrotum should be more deeply pigmented than the surrounding skin (Cavaliere, 2019).
- *Females:* The labial, inguinal, and suprapubic areas are inspected and palpated to detect masses, swelling, or bulges. The clitoris should be located superior to the vaginal opening. Hymenal tags and mucous/bloody vaginal discharges are benign, transient findings.

Edema of the genitalia is common in both sexes in breech deliveries. It may also be due to the effects of transplacentally acquired maternal hormones. The perineum should be smooth and should have no dimpling, fistulae, or discharges (Cavaliere, 2019; Gardner & Hernandez, 2016).

The anus is evaluated for patency and tone. Patency can be documented by gentle insertion of a soft rubber catheter. The passage of meconium does not confirm a patent anus, because meconium may be passed through a fistulous tract (Fletcher, 1998; Parry, 2015). Gentle stroking of the anal area should produce constriction of the sphincter, known as the anal wink (Goodwin, 2019).

Back. The infant should be placed in the prone position while the back is examined for curvature, patency, and presence of structural abnormalities. Vertebrae are palpated for enlargement and pain. Symmetry should be seen on both sides of the back and between the two scapulae. The spine should be straight and flexible and should have no visible defects, such as pits, hair tufts, or dimples (Tappero, 2019).

Extremities and Hips. The extremities are observed for symmetry, degree of flexion, and presence of defects and fractures. Full range of motion should be present, and the extremities should move symmetrically. Although symmetry of gluteal skin folds suggests normal hips, the Ortolani and Barlow maneuvers should be performed to confirm the stability of the hips (Figure 4.14). The Ortolani maneuver reduces a dislocated femoral head into the acetabulum, and the Barlow maneuver reflects the ability of the femoral head to be dislocated (Tappero, 2019).

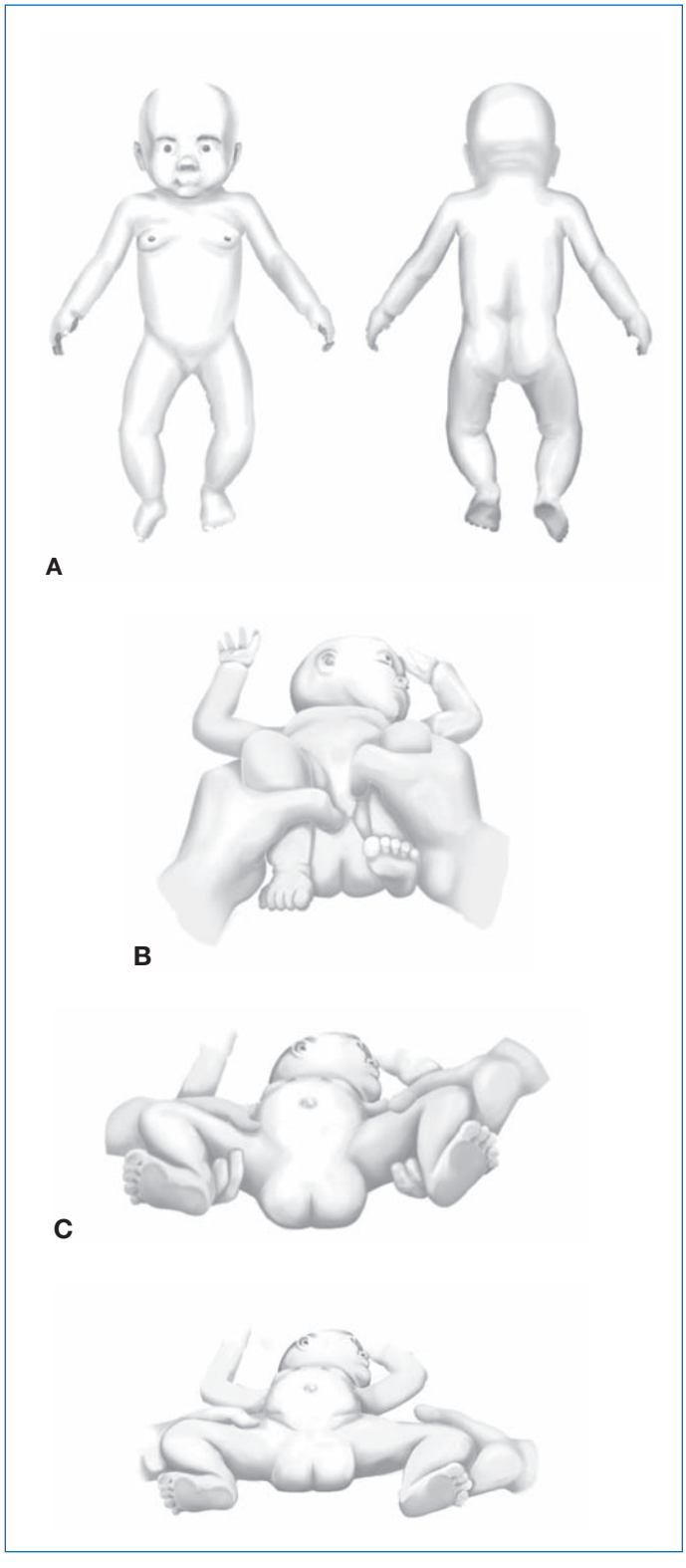


FIGURE 4.14 Signs of congenital dislocation of hip. (A) Asymmetry of gluteal and thigh folds, (B) Barlow maneuver, and (C) Ortolani maneuver.

Source: Based on Lewis, S. M., Bucher L., Heitkemper, M. M., Harding, M. M., Kwong, J., & Roberts, D. (2017). *Medical-surgical nursing: Assessment and management of clinical problems* (10th ed.). St. Louis, MO: Elsevier.

The limbs should be equal in length, and they should be in proportion to the body; they also should be straight and should have no

TABLE 4.11

ASSESSMENT OF NEONATAL REFLEXES

Reflex	Technique	Response	Comments
Asymmetric tonic neck	With infant supine and in light sleep or quiet awake state, turn head to right until jaw is over shoulder; hold for 15 seconds, then release.	Occipital flexion and mental extension; right arm and leg are extended; left arm and leg are flexed. Premature neonates may lie at rest in this position for extended periods.	Reflex appears at 35 weeks gestation and disappears by 6–7 months of age.
Babinski	Using thumbnail, scratch sole of foot at lateral side from toes to heel.	Dorsal flexion of great toe with extension of other toes.	Care must be taken not to elicit plantar grasp by stimulating sole of foot. Reflex appears at 34–36 weeks gestation, is well established at 38 weeks, and disappears at 12 months of age.
Doll's eyes	Rotate head from side to side, observing eye movement.	As head is moved to right or left, eyes move in opposite direction.	Lack of eye movement with head rotation or movement of eyes in same direction as head may indicate brainstem or oculomotor nerve dysfunction. Reflex is well established and may even be exaggerated at 24–25 weeks' gestation.
Galant (truncal incurvation)	Place infant prone, either lying on flat surface or in suspension; lightly stroke along either side of spinal column from shoulder to buttocks.	Normal response is strong incurvation of whole vertebral column toward stimulated side.	Reflex is first seen at 28 weeks' gestation.
Glabellar	Hold head firmly and tap forehead just above nose.	Normal response is tighter closure of both eyes and wrinkling of brow.	Asymmetry, absent or exceptionally strong response (closure longer than 1 second), or generalized startle is abnormal.
Moro	Hold infant suspended over mattress, supporting head with one hand and body with other hand; rapidly lower both hands 10–20 cm without flexing neck, but do not allow baby to drop back to mattress.	Symmetric abduction of arms and extension at elbows with hands open completely, followed by adduction of arms and flexion at elbows with curling of fingers; infant cries or grimaces at conclusion.	Response attenuates and ultimately disappears with repetition as habituation occurs. No response is seen at <26 weeks' gestation; extension only at 30 weeks; variable adduction at 34 weeks; complete response at 38 weeks. Reflex disappears at 6 months of age.
Palmar grasp	Stimulate palmar surface of hand with a finger.	Neonate grasps finger; grasp tightens with attempt to remove finger.	Reflex appears at 28 weeks' gestation, is well established after 32 weeks, and disappears at 2 months of age.
Pupillary	Elicit in darkened environment by presenting bright, sharply focused light from periphery.	Pupils constrict equally.	Reflex is sluggish but present between 28 and 32 weeks' gestation in healthy neonates; it is fully present after 34 weeks.
Rooting	Stroke cheek and corner of mouth.	Mouth opens and head turns toward stimulus.	Reflex appears at 28 weeks' gestation, followed by long latency period beginning at 30 weeks; it is well established at 32–34 weeks and disappears by 3–4 months of age.
Stepping	Hold neonate upright and allow feet to touch flat surface.	Alternating stepping movements.	Reflex appears at 35–36 weeks gestation, is well established at 37 weeks, and disappears at 3–4 months of age.
Sucking	Touch or stroke lips.	Mouth opens, and neonate begins to suck.	Reflex appears at 28 weeks' gestation, is well established by 32–34 weeks, and disappears at 12 months of age.

Source: Data from Heaberlin, P. D. (2019). Neurologic assessment. In E. P. Tappero & M. E. Honeyfield (Eds.), *Physical assessment of the newborn* (6th ed., pp. 167–192.). New York, NY: Springer Publishing Company.

edema or crepitus. Palpation or movement of the limbs should not produce a painful response. The digits should be equally spaced and have no webbing. The nails should extend to the end of the nail beds.

Reflexes. The most common neonatal reflexes are presented in Table 4.11.

Variations and Abnormal Findings on Physical Examination

Minor variations and abnormal findings of the physical examination are presented in Table 4.12.

TABLE 4.12

ABNORMALITIES AND VARIATIONS FOUND ON PHYSICAL EXAMINATION OF NEWBORNS AND INFANTS

Finding	Definition/Description	Comments
Skin		
Color	Acrocyanosis (blue discoloration of the hands, feet, and perioral area), commonly seen in the first 6–24 hours of life.	Occurs when blood flow to an area is sluggish and all available oxygen has been extracted (Carley & Duderstadt, 2019); exacerbated by cooling and diminished by warming; normal variation but abnormal if persists beyond the first 24 hours of life.
	Cutis marmorata (mottling of the skin in response to cold or other stressful stimuli); caused by dilation of capillaries, usually greatest on the extremities but may be seen on the trunk.	May be suggestive of other conditions (e.g., cardiovascular hypertension, hypothyroidism) if mottling is extensive, shows no improvement with warming, or persists beyond first few months (Fletcher, 1998; Vargo, 2019).
	Cyanosis (blue discoloration of the skin, tongue, and mucous membranes).	Caused by excess of desaturated hemoglobin in the blood (cardiopulmonary disease) or a structural defect in the hemoglobin molecule (methemoglobin); always an abnormal finding.
	Jaundice (yellow coloring of the skin, mucous membranes, and sclerae).	Caused by deposition of bilirubin; may be physiologic.
	Pallor (absence of color or paleness of the skin).	Caused by a decrease in cardiac output, subcutaneous edema, anemia, or asphyxia (Lissauer, 2015).
	Plethora (ruddy skin coloration in the newborn).	Caused by high circulating red blood cell volume (abnormal finding).
Lesions	Café au lait spots (light tan or brown macules with well-defined borders, representing areas of increased epidermal melanosis); except for deeper pigmentation, appearance is not different from that of surrounding skin.	More common in normal infants of color. Six or more macules, regardless of spots' size or infant's race, may be pathologically significant, especially if located in the axilla.
	Cutis aplasia (localized or widespread foci of absence of some or all layers of skin); defect may be covered by a thin, translucent membrane or scar tissue, or area may be raw and ulcerated.	Occurs predominantly on the scalp and less frequently on the limbs and trunk (Hoath & Narendran, 2015).
	Ecchymosis (nonblanching purple or blue-black macule larger than 2 mm in diameter); represents extravasation of blood into subcutaneous tissue.	Results from trauma to underlying blood vessels or fragility of the vessel walls.
	Erythema toxicum (white or yellow papules on red macular base), commonly found on face, trunk, or proximal extremities but not on hands or feet.	Common, benign finding; vesicles are rare, sterile, and composed primarily of eosinophils (Witt, 2019). When vesicles are pronounced or coalescent, they may mimic postural infectious rash.

(*continued*)

TABLE 4.12

ABNORMALITIES AND VARIATIONS FOUND ON PHYSICAL EXAMINATION OF NEWBORNS AND INFANTS (*continued*)

Finding	Definition/Description	Comments
	Harlequin fetus (most severe form of congenital ichthyosis; skin is completely covered with thick, horny scales resembling armor that are divided by deep red fissures).	Most such infants die of dehydration, infection, or respiratory insufficiency within a few hours or days (Hoath & Narendran, 2015).
	Harlequin sign (vascular phenomenon represented by distinct midline demarcation in side-lying infants; dependent half is deep red, upper half is pale).	Benign finding that lasts a few seconds to 30 minutes, occasionally reverses when position is changed. The physiologic basis is unidentified; without pathologic significance. Occurs most frequently in LBW neonates (Hoath & Narendran, 2015; Witt, 2019).
	Strawberry hemangioma (red, raised, circumscribed, soft, compressible, lobulated tumor; may occur anywhere on the body).	Benign tumor of the vascular endothelium that has a proliferative and an involutional phase; most involute spontaneously. Treatment is unnecessary unless vital functions are affected (Hoath & Narendran, 2015; Witt, 2019).
	Cavernous hemangioma (similar to strawberry hemangioma; involves dermis and subcutaneous tissue and is soft and compressible on palpation; overlying skin is bluish-red in color).	Cavernous lesions may cause thrombocytopenia (Kasabach–Merritt syndrome) or hypertrophy of bone and soft structures of extremities (Klippel-Trenaunay-Weber syndrome; Hoath & Narendran, 2015; Witt, 2019).
	Mongolian spot (blue-black macule, lacking a sharp border, most frequently seen on sacrum, buttocks, flanks, or shoulders).	Benign lesion, common in dark-skinned neonates, resulting from delayed disappearance of dermal melanocytes; lesion gradually disappears during the first years of life (Witt, 2019).
	Milia (1 mm, pearly white or yellow papules without erythema; in the mouth these are called Epstein's pearls).	Epidermal inclusion cysts caused by blockage of sebaceous glands; a benign finding that resolves during the first weeks of life (Witt, 2019).
	Miliaria—three types 1. Crystallina (1–2 mm, thin-walled vesicles with nonerythematous and nonpigmented base [without inflammation]). 2. Rubra—small, erythematous, grouped papules [prickly heat]). 3. Pustulosis or profunda (nonerythematous pustules).	Lesions caused by blockage of sweat glands. They are exacerbated by a warm, humid environment and most frequently develop in intertriginous areas and over the face and scalp. They resolve when the environmental factors are eliminated (Hoath & Narendran, 2015; Witt, 2019).
	Neonatal pustular melanosis (small, superficial vesiculopustules with little or no surrounding erythema; crusted or scaly collarettes appear after vesicles rupture; lesions eventually resolve into hyperpigmented areas).	Transient and benign; frequently confused with infectious lesions. Smears of pustular material reveal predominantly neutrophils and no bacteria. (Hoath & Narendaran, 2015; Witt, 2019).
	Salmon patch (nevus; dull, pink-red, irregularly shaped macules that blanch on pressure; commonly found on nape of neck [stork bite], glabella, forehead, eyelids, and upper lip).	Benign finding; lesions are composed of distended, dilated capillaries, and most lesions (except those on the neck) disappear by 1 year of age (Witt, 2019).
	Port wine stain (nevus, macular lesion; present at birth but may be pale and hard to discern; initially pink in color with sharply delineated borders; progresses to dark red/purple; some develop small, angiomatous nodules).	Developmental vascular malformation that occurs mostly on the face; does not increase in size but grows with the infant; may occur alone or with structural anomalies (e.g., Sturge–Weber syndrome; Hoath & Narendran, 2015; Witt, 2019).

(*continued*)

TABLE 4.12

ABNORMALITIES AND VARIATIONS FOUND ON PHYSICAL EXAMINATION OF NEWBORNS AND INFANTS (*continued*)

Finding	Definition/Description	Comments
	Petechiae (tiny red or purple, nonblanching macules that range from pinpoint to pin head size).	Caused by minute hemorrhages in the dermal or submucosal layers; may be benign and self-limiting or pathognomonic of serious underlying conditions. They are benign when found on presenting part and when localized areas appear at the same time; progressive, widespread areas require evaluation (Fletcher, 1998; Witt, 2019).
Redundant skin	More skin than is necessary or normally present in a particular area.	Seen in the neck after resolution of cystic hygroma or in the abdomen in a neonate with prune belly syndrome.
Sclerema neonatorum	Diffuse, stone-hard, nonpitting cutaneous induration; overlying skin appears pale and waxy; face has a mask-like appearance; joints are stiff.	Occurs in debilitated neonates; diffuse systemic process with grave prognosis (Hoath & Narendran, 2015).
Subcutaneous fat necrosis	Firm, nonpitting, poorly circumscribed, reddish violet lesions appearing in the first weeks of life on the face, arms, trunk, thighs, and buttocks. Affected areas may be slightly elevated above adjacent skin (Mangurten, Puppala, & Prazad, 2015).	Most often seen in areas where a fat pad is present. May occur secondary to cold or trauma and sometimes accompanied by hypercalcemia (Hoath & Narendran, 2015).
Head and Neck		
Acrocephaly	Congenital malformation of the skull caused by premature closure of the coronal and sagittal sutures; accelerated upward growth of the head gives it a long, narrow appearance with a conic shape at the top (also called oxycephaly).	May be associated with premature closure of sutures; found with certain syndromes (e.g., Crouzon's, Apert's; Robinson & Cohen, 2015a).
Anencephaly	Failed closure of the anterior neural tube without skull formation; the brain is severely malformed, lacking definable structure, although a rudimentary brainstem usually is present.	Most affected neonates (75%) are stillborn; without intervention; the remainder die in the neonatal period (Gressens & Huppi, 2015; Robinson & Cohen, 2015a).
Brachycephaly	Congenital malformation of the skull caused by premature closure of the coronal suture; excessive lateral growth of the head gives it a short, broad appearance.	Condition found with certain syndromes (e.g., trisomy 21, Apert's; Robinson & Cohen, 2015a).
Bruit	Abnormal murmur-like sound heard on auscultation of an organ or gland that is caused by dilated, tortuous, or constricted vessels. The specific character of the bruit, its location, its association with other clinical findings, and the time of occurrence in a cycle of other sounds is of diagnostic importance.	Bruits heard over the fontanelle or lateral skull associated with signs of congestive heart failure may denote intracranial arteriovenous malformation (Heaberlin, 2019; Johnson, 2019).
Caput succedaneum	Vaguely demarcated pitting edema of the scalp that may extend across suture lines and can shift in response to gravity.	Benign finding that appears at birth (from pressure of the maternal cervix on the fetal skull) and resolves in a few days (Mangurten et al., 2015).

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TABLE 4.12

ABNORMALITIES AND VARIATIONS FOUND ON PHYSICAL EXAMINATION OF NEWBORNS AND INFANTS (*continued*)

Finding	Definition/Description	Comments
Cephalohematoma	Extradural fluid collection caused by bleeding between the skull and periosteum; generally occurs over one or both parietal bones and does not cross the suture lines; has distinct margins and may be fluctuant or tense.	1. May form during labor and enlarges for the first 12–24 hours; most resolve spontaneously over several weeks to months (Johnson, 2019; Johnson, 2017). 2. Linear skull fracture is found in 5% of unilateral and 18% of bilateral lesions (Abdulhayoglu, 2017; Johnson, 2019; Mangurten et al., 2015). 3. May result in hyperbilirubinemia (Mangurten et al., 2015).
Craniosynostosis	Premature closure of one or more cranial sutures, causing abnormal skull shape and possibly a palpable ridge along the suture line.	Head growth is restricted in the area perpendicular to the stenotic suture and is excessive in unrestricted areas. Most cases are isolated events, but the condition can occur in some syndromes (Robinson & Cohen, 2015a).
Craniotabes	Congenital thinness of bone at the top and back of the head. Bones may collapse with gentle pressure and recoil (ping-pong).	1. May be a normal variant if present to a mild degree near suture lines. May be caused by the pressure of the skull against the maternal pelvic brim; spontaneous resolution usually occurs in a few weeks (Fletcher, 1998). 2. May be associated with congenital syphilis and other congenital conditions (osteogenesis imperfecta); due to bone resorption or delay in ossification (Walker, 2018).
Dolichocephaly or scaphocephaly	Congenital malformation of the skull in which premature closure of the sagittal suture results in restricted lateral growth.	Long, narrow head (Robinson & Cohen, 2015a).
	Skull shape often seen in premature babies as a result of prolonged positioning with head turned to the side.	
Encephalocele	Protrusion of brain tissue through a congenital defect in the cranium; most often occurs in the occipital midline but may also be seen in the frontal, temporal, or parietal areas.	Other cranial defects, congenital anomalies (hydrocephalus, microcephaly, craniosynostosis), and autosomal recessive syndromes (Walker–Warburg) are frequently seen (Gressens & Huppi, 2015).
Hair whorls	Two or more hair whorls, or abnormally placed whorls (other than parietal area).	May indicate brain anomaly; it has been postulated that the pattern of hair development correlates with underlying brain development (Johnson, 2019).
Macrocephaly	Excessive head size in relation to weight, length, and GA. OFC is over 90th percentile.	1. Familial; facial features usually are normal. 2. May reflect pathologic condition (e.g., hydrocephaly, hydranencephaly) or chromosomal or neuroendocrine disorder (Bauer-Huang & Doherty, 2018).
Microcephaly	Abnormally small head size relative to weight, length, and GA. OFC is under 10th percentile.	Associated with either microcephaly (marked reduction in size of brain or cerebral hemispheres) or acquired brain atrophy.
Molding	Process by which the head shape is altered as the fetus passes through the birth canal.	Benign finding; condition usually resolves during the first few postnatal days.
	The biparietal diameter becomes compressed, the head is elongated, and the skull bones may overlap at the suture lines.	
Neck masses	May be detected on palpation or inspection.	Most common neck mass; caused by development of sequestered lymph channels, which dilate into cysts (Lissauer, 2015; Johnson, 2019).

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TABLE 4.12

ABNORMALITIES AND VARIATIONS FOUND ON PHYSICAL EXAMINATION OF NEWBORNS AND INFANTS (*continued*)

Finding	Definition/Description	Comments
	Cystic hygroma (soft, fluctuant mass that is easily transilluminated; usually laterally placed or over clavicles).	
	Goiter (anterior mass caused by hypothyroidism).	Rare in neonates (Johnson, 2019).
	Thyroglossal duct cyst/branchial cleft cyst; a mass may be found high in the neck.	Rare in neonates (Johnson, 2019).
Plagiocephaly	Asymmetry of the skull due to flattening of the occiput. Can be deformational (positional) or due to premature or irregular closure of the coronal or lambdoidal sutures.	1. Posterior plagiocephaly almost always due to mechanical forces (positional; "back to sleep"). 2. Anterior plagiocephaly most commonly due to premature fusion of the sutures (Robinson & Cohen, 2015a).
Subgaleal	Bleeding into the potential space between the epicranial aponeurosis and the periosteum of the skull; manifests as a firm to fluctuant scalp mass with poorly demarcated borders that may extend onto the face, forehead, or neck and may be accompanied by signs of hypovolemia.	May be a life-threatening condition; can be caused by hemorrhage coagulopathy, asphyxia, or vacuum extraction (Mangurten et al., 2015).
Webbed neck	Redundant skin at posterolateral region of neck.	Found with Turner's, Noonan's, and Down syndromes (Bennett & Meier, 2019).
Face		
Asymmetry	Unequal appearance or movement of mouth and lips; unequal closure of eyes; uneven appearance of nasolabial folds.	Often caused by in utero positioning but may be due to facial nerve paresis; in mild cases may be evident only with crying (affected side fails to move or moves less when infant cries).
Ears		
Auricular appendage	Accessory tragi, most commonly in pretragal area; may occur within or behind the ear. These structures contain cartilage and are not truly skin tags.	Primarily of cosmetic significance unless accompanied by other diffuse malformations. Seen in certain congenital syndromes (e.g., Goldenhar's, Treacher Collins); hearing assessment is indicated when other anomalies are present (Johnson, 2019; Parikh & Mitchell, 2015).
Auricular sinus	Narrow, fistulous tract most often located directly anterior to helix.	May be familial or may be associated with microtia, auricular appendage, facial cleft syndromes, and syndromic anomalies of the outer ear (Parikh & Mitchell, 2015; Spilman, 2002).
Low-set ears	Superior attachment of pinna lies below imaginary line drawn between both inner canthi and extended posteriorly.	May be associated with chromosomal or renal anomalies (Lewis, 2014a, b).
Microtia	Severely misshapen, dysplastic external ear.	Frequently associated with other malformations that result in conductive hearing loss (i.e., atresia of auditory meatus, abnormalities of middle ear; Parikh & Mitchell, 2015; Walker, 2018).

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TABLE 4.12

ABNORMALITIES AND VARIATIONS FOUND ON PHYSICAL EXAMINATION OF NEWBORNS AND INFANTS (*continued*)

Finding	Definition/Description	Comments
Eyes		
Blepharophimosis	Narrow palpebral fissures in the horizontal measurement; also known as short palpebral fissures.	Usually caused by lateral displacement of the inner canthi; seen in certain dysmorphic or chromosomal syndromes (Fletcher, 1998; Orge & Grigorian, 2015).
Brushfield spots	Pinpoint white or light yellow spots on the iris.	Seen in 75% of neonates with Down syndrome but may also be a normal variant; not always visible at birth (Johnson, 2019; Orge & Grigorian, 2015).
Coloboma	Cleft-shaped defect in ocular tissue (eyelid, iris, ciliary body, retina, or optic nerve).	Result of incomplete embryologic closure of ocular structures; may be an isolated finding or part of a malformation syndrome (CHARGE, trisomies 13, 18, 22; Bennett & Meier, 2019; Orge & Grigorian, 2015).
Ectropion	Eversion of the margin of the eyelid, which leaves the conjunctiva exposed.	Seen in facial nerve paralysis, in certain syndromes, and in harlequin fetus and collodion baby (Fletcher, 1998; Orge & Grigorian, 2015).
Entropion	Inversion of the eyelid; eyelashes may be in contact with the cornea and conjunctiva.	Congenital condition that usually resolves spontaneously without damage (Fletcher, 1998; Lissauer, 2015; Orge & Grigorian, 2015).
Epicanthal folds	Vertical fold of skin at the inner canthus on either side of the nose.	A feature of normal fetal development and may be present in normal infants. Characteristic of trisomy 21 but may occur in malformation syndromes, especially those with a flat nasal bridge; may also be a physical manifestation of in utero compression (Potter facies; Parikh & Mitchell, 2015).
Exophthalmos	Abnormal displacement of the eye characterized by protrusion of the eyeball.	May be caused by increased volume of the orbit (tumor), swelling secondary to edema or hemorrhage, endocrine disorder (e.g., Graves' disease, hyperthyroidism); known as proptosis when accompanied by shallow orbits (Crouzon's disease; Fletcher, 1998; Orge & Grigorian, 2015).
Hypertelorism	Increased distance between the orbits, observed clinically as a large interpupillary distance (see Telecanthus; Parikh & Mitchell, 2015).	Frequently seen in craniofacial syndromes (Orge & Grigorian, 2015).
Hypotelorism	Decreased distance between the orbits, observed clinically as smaller than normal interpupillary distance (Parikh & Mitchell, 2015).	Frequently seen in trisomies 13 and 21 and in other syndromes (Orge & Grigorian, 2015).
Leukocoria	White pupil, denoting an abnormality of the lens, vitreous, or fundus; an indication for further evaluation (Orge & Grigorian, 2015).	May be seen on direct visualization, or as absence of a red reflex; most commonly seen in cataracts; also found in retinoblastoma, retinal detachment, and vitreous hemorrhage.
Microphthalmia	Small eye; diameter measures less than two-third of the normal 16 mm at birth (Orge & Grigorian, 2015).	Can be hereditary or caused by chromosomal anomalies and environmental influences during development. Associated with multisystem conditions or syndromes (e.g., CHARGE, trisomy 13, fetal rubella effects).

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TABLE 4.12

ABNORMALITIES AND VARIATIONS FOUND ON PHYSICAL EXAMINATION OF NEWBORNS AND INFANTS (*continued*)

Finding	Definition/Description	Comments
Nystagmus	Involuntary, rhythmic movements of the eye; may be horizontal, vertical, rotary, or mixed. Optokinetic nystagmus reflexive response to a moving target.	Occasional, intermittent nystagmus in an otherwise healthy newborn may be normal in the neonatal period; however, it must be evaluated if frequent or persistent (or both). Pathologic forms may be due to ocular, neurologic, or vestibular defects (Orge & Grigorian, 2015).
Ptosis (blepharoptosis)	Abnormal drooping of one or both upper eyelids; lid does not rise to normal level.	Caused by congenital or acquired weakness in the levator muscle or paralysis of the third cranial nerve; may be difficult to detect in neonates unless unilateral with asymmetry between the eyelids (Orge & Grigorian, 2015).
Strabismus	Misalignment of the visual axes: Esotropia—crossed eyes Exotropia—wall eye.	Refer for ophthalmologic evaluation if present by third month of age. Results from inheritance, paralysis of the lateral rectus muscle, or refractive errors; may be due to diseases that reduce visual acuity in one eye (Orge & Grigorian, 2015).
Subconjunctival hemorrhage	Bright red area on sclerae.	Caused by rupture of a capillary in the mucous membrane that lines the conjunctiva; commonly seen after vaginal delivery, does not reflect ocular trauma unless massive and associated with other findings; usually resolves in 7–10 days (Mangurten et al., 2015).
Synophrys	Meeting of the eyebrows in the midline.	Seen in multisystem conditions or syndromes (e.g., Cornelia de Lange's, congenital hypertrichosis; Parikh & Mitchell, 2015).
Telecanthus	Lateral displacement of the inner canthi; eyes appear too widely set because of a disproportionate increase between the inner canthi; interorbital distance is appropriate (Parikh & Mitchell, 2015).	Evident in fetal alcohol syndrome and other syndromes; not synonymous with hypertelorism, although its presence can lead to a false impression of hypertelorism (Sharma, 2014).
Nose		
Choanal atresia	Obstruction of posterior nasal passages.	Patency is assessed in the quiet state. If condition is bilateral, neonate is cyanotic at rest and pink when crying; if unilateral, baby is unable to breathe if mouth is held closed and unaffected naris is occluded with examiner's finger. Atresia/stenosis may be confirmed by passing a catheter.
Nasal deformation	May result from pressure in utero.	Benign condition that resolves in a few days.
	May be due to dislocation of the septal cartilage.	Attempts to restore normal anatomy are unsuccessful; nares remain asymmetric when tip of nose is compressed (Johnson, 2019; Mangurten et al., 2015).
Mouth		
Cleft lip/palate	Failure of midline fusion during first trimester.	May occur alone or with other malformations.
Epstein's pearls	Small, white, pearl-like inclusion cysts that appear on the palate and gums.	Benign finding that disappears spontaneously by a few weeks of age (Johnson, 2019).

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TABLE 4.12

ABNORMALITIES AND VARIATIONS FOUND ON PHYSICAL EXAMINATION OF NEWBORNS AND INFANTS (*continued*)

Finding	Definition/Description	Comments
Micrognathia	Underdevelopment of the jaw, especially the mandible.	Dysmorphic feature seen in certain malformation syndromes (e.g., Pierre Robin sequence; Bennett & Meier, 2019; Johnson, 2019).
Thorax/Chest		
Asymmetry	May be unequal in shape or excursion.	1. Asymmetric shape caused by positioning in utero or presence of air trapping or space-occupying lesions. 2. Unequal excursion caused by diaphragmatic hernia, phrenic nerve damage, or air leakage or trapping (Fraser, 2019).
Auscultation	Adventitious breath sounds	Fraser (2019).
	Crackles	Discrete, noncontinuous bubbling sounds during inspiration; classified as fine, medium, or coarse. Previously called rales.
	Rhonchi	Continuous, nonmusical, low-pitched sounds occurring on inspiration and expiration; caused by secretions or aspirated matter in large airways.
	Stridor	Rough, harsh sounds caused by narrowing of upper airways; present during both phases of respiratory cycle but worse during inspiration; common with laryngomalacia, subglottic stenosis, and vascular ring.
	Wheezes	Musical, high-pitched sound generated by air passing at high velocity through a narrowed airway; heard most often on expiration but can be noted during both phases of respiratory cycle if airway diameter is restricted and fixed.
	Grunting	Sound produced by forceful expiration against a closed glottis; compensatory mechanism to prevent or reverse alveolar collapse.
	Murmur	Grades I through VI assigned depending on intensity and presence of thrill.
Barrel chest	Increased anteroposterior diameter of the chest.	Result of air trapping in the pleural space (pneumothorax) or distal airways (aspiration or pneumonia), space-occupying lesions, or over distention from mechanical ventilation (Fletcher, 1998; Fraser, 2019).
Heave	Diffuse, gradually rising impulse seen in the anterior chest overlying the ventricular area. A **parasternal heave** is a precordial impulse that may be felt (palpated) in patients with cardiac or respiratory disease. Precordial impulses are visible or palpable pulsations of the chest wall, which originate on the heart or the great vessels.	Can be associated with hypertrophied ventricles or volume overload (Felner, 1990).
Pectus carinatum	Deformation of chest wall caused by protuberant sternum; also called pigeon chest.	May be associated with Marfan, Noonan's, and other syndromes (Fraser, 2019).

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TABLE 4.12

ABNORMALITIES AND VARIATIONS FOUND ON PHYSICAL EXAMINATION OF NEWBORNS AND INFANTS (*continued*)

Finding	Definition/Description	Comments
Pectus excavatum	Deformation of chest wall caused by depressed sternum; also called funnel chest.	May be associated with Marfan, Noonan's, and other syndromes (Fraser, 2019); may develop after birth in neonates with laryngomalacia.
Retractions	Drawing in of the soft tissues of the chest between and around the firmer tissue of the cartilaginous and bony ribs; seen in intercostal, subcostal, substernal, and suprasternal areas.	Mild subcostal retractions may be seen in healthy newborns; intercostal, substernal, and suprasternal retractions reflect increased work of breathing and suggest respiratory distress.
Supernumerary nipples (polythelia)	Extra nipples; may appear as slightly pigmented linear dimples or may be more defined, with palpable breast nodules.	Normal variant; nipples appear along the mammary line. Prospective studies have refuted the association with renal anomalies; no indication for further evaluation based solely on the presence of supernumerary nipples.
Abdomen		
Abdominal wall defects	Exstrophy of the bladder (protrusion and eversion of the bladder through an embryologic defect, resulting in absence of muscle and connective tissue on the anterior abdominal wall).	Often associated with other defects of the GU and musculoskeletal systems and the GI tract (Cavaliere, 2019; Zderic, 2005).
	Gastroschisis (protrusion of viscera through an abdominal wall defect arising outside the umbilical ring; the cord therefore is not inserted on the defect, and the herniated organs are not covered by peritoneum).	Defect usually is to the right of the umbilicus (Goodwin, 2019; Parry, 2015).
	Omphalocele (herniation of viscera through an abdominal wall defect within the umbilical ring; defect usually is covered by a translucent, avascular sac at the base of the umbilicus).	Umbilical cord always inserts into the sac; occasionally, the sac may rupture. Defect usually is larger than 4 cm and may be associated with other congenital defects and chromosomal anomalies (Goodwin, 2019; Parry, 2015).
	Umbilical hernia (failure of the umbilical ring to contract, allowing protrusion of bowel or omentum through the abdominal wall).	Characterized by a fascial defect smaller than 4 cm and intact umbilical skin (Fletcher, 1998; Parry, 2015).
Bruit	See section under Head and Neck	Persistence after a position change may indicate abnormalities of the umbilical vein or hepatic vascular system, hepatic hemangioma, or renal artery stenosis (Goodwin, 2019).
Diastasis rectus	Midline bulge from xiphoid to umbilicus, seen when abdominal muscles are flexed.	Caused by separation of the two rectus muscles along the median line of the abdominal wall; a common benign finding in newborns that has no clinical significance; resolves without intervention (Goodwin, 2019).
Distention	Increase in abdominal girth caused by an increase in the volume of intraperitoneal, thoracic, or pelvic contents.	May be pathologic or benign. Pathologic causes include GI obstruction, ascites, abdominal mass, organomegaly, and depression of the diaphragm (tension pneumothorax). Benign causes include postprandial state, crying, swallowing of air with feedings, air leakage with mechanical ventilation, and administration of CPAP.

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TABLE 4.12

ABNORMALITIES AND VARIATIONS FOUND ON PHYSICAL EXAMINATION OF NEWBORNS AND INFANTS (*continued*)

Finding	Definition/Description	Comments
Patent urachus	Postnatal persistence of communication between the urinary bladder and the umbilicus; may result in passage of urine from the umbilicus, which otherwise appears normal. Other signs are a large, edematous cord that fails to separate after the normal interval and retraction of the umbilical cord during urination.	Lower urinary tract obstruction should be considered (Cavaliere, 2019).
Prune belly syndrome	Congenital deficiency of abdominal musculature, characterized by a large, flaccid, wrinkled abdomen, cryptorchidism, and GU malformations.	Almost always seen in males (Vogt & Dell, 2015).
Scaphoid abdomen	Abdomen with a sunken anterior wall.	May be present with a diaphragmatic hernia or malnutrition.
Single umbilical artery		Seen in fewer than 1% of neonates; ~40% of affected newborns have other major congenital malformations. When condition occurs without other abnormalities, it usually is a benign finding (Lissauer, 2015).
Genitalia/Perineum		
Ambiguous	Presence of a phallic structure not discretely male or female, abnormally placed urethral meatus, and inability to palpate one or both gonads in a male.	May be associated with serious endocrine disorders; rapid evaluation and diagnosis are critical (Al Remeithi & Wherrett, 2015; Cavaliere, 2019).
Anal atresia	Absence of an external anal opening; imperforate anus.	Infant may fail to pass meconium; however, meconium may be passed through a rectovaginal or rectovestibular fistula in a female or rectoperineal or rectourethral fistula in a male (Goodwin, 2019).
Chordee	Ventral or dorsal curvature of the penis; most evident on erection.	May occur alone but often accompanies hypospadias (Cavaliere, 2019; Palmer & Palmer, 2016).
Clitoromegaly	The appearance of an enlarged clitoris, with no regard to cause (Al Remeithi & Wherrett, 2015); it may be swollen, enlarged, widened, or merely prominent, as in premature females.	May be a normal finding in a premature female or may represent masculinization from exposure to excess androgens during fetal life.
Cryptorchidism	Testis or testes in extrascrotal location (undescended testis or testes); characterized by empty, hypoplastic scrotal sac.	In most cases descent occurs spontaneously by 6–9 months of age; descent after 9 months is rare. Bilateral cryptorchidism occurs in up to 30% of patients; consider disorder of sexual differentiation until proven otherwise (Al Remeithi & Wherrett, 2015; Cavaliere, 2019; Palmer & Palmer, 2016).
Epispadias	Abnormal location of urethral meatus on the dorsal surface of the penis; abnormal urine stream may be seen.	Varies in severity from mild (glanular) to complete version seen in exstrophy of the bladder; all forms are associated with dorsal chordee; may require evaluation by a urologist before circumcision (Palmer & Palmer, 2016; Vogt & Dell, 2015).
Hydrocele	Nontender scrotal swelling caused by fluid collection; arises from passage of peritoneal fluid through patent processus vaginalis.	May be seen with inguinal hernia but can be distinguished from hernia because hydrocele appears translucent on transillumination; entire circumference of testis may be palpated; and it cannot be reduced (Cavaliere, 2019; Elder, 2016; Palmer & Palmer, 2016).

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TABLE 4.12

ABNORMALITIES AND VARIATIONS FOUND ON PHYSICAL EXAMINATION OF NEWBORNS AND INFANTS (*continued*)

Finding	Definition/Description	Comments
Hydrocolpos/ hydrometrocolpos	Manifests as suprapubic mass or protruding perineal mass as a result of accumulation of secretions in vagina or vagina and uterus.	Caused by excessive intrauterine stimulation by maternal estrogens, with obstruction of the genital tract by an intact hymen, hymenal bands, vaginal membrane, or vaginal atresia (Cavaliere, 2019; Karfer, 2016).
Hymenal tag	Redundant tissue manifesting as an annular tag protruding from the vagina.	Benign finding; most disappear during the first year of life.
Hypospadias	Abnormal location of urethral meatus on the ventral surface of the penis; caused by incomplete development of the anterior urethra; abnormal urine stream may be seen.	Urethral opening may be found on the glans, scrotum, or perineum. Infants with penoscrotal or perineal type or with glanular form and other genital anomalies or dysmorphic features should be evaluated to rule out disorders of sexual differentiation (Al Remeithi & Wherrett, 2015). Evaluation by a urologist may be required before circumcision.
Inguinal hernia	Scrotal mass caused by the presence of loops of intestines in the scrotal sac; arises from persistence of processus vaginalis, often associated with hydrocele.	On examination, the entire circumference of the testis is not palpable, and the scrotum cannot be transilluminated. Unless incarcerated, hernias are reducible (Cavaliere, 2019; Elder, 2016).
Micropenis/ microphallus	Abnormally short or thin penis.	Penis more than two standard deviations below the mean of length and width for age according to standard charts; frequently requires evaluation by an endocrinologist and a geneticist (Al Remeithi & Wherrett, 2015).
Phimosis	Intractable foreskin.	Must be differentiated from physiologic phimosis, a nonretractable foreskin that is a normal finding in neonates (Cavaliere, 2019).
Priapism	Constantly erect penis.	Abnormal finding in neonate (Broderick, 2016; Cavaliere, 2019).
Retractile testis	Normally descended testis that recedes into the inguinal canal because of activity of the cremaster muscle.	May not be seen in the newborn period because of lack of cremaster reflex in this age group; however, some newborns do demonstrate this response (Cavaliere, 2019; Elder, 2016).
Testicular torsion	Twisting of the testis or testes on the spermatic cord; manifests as a swollen, red or bluish-red scrotum; may be painful, but this is not a universal symptom in the neonate.	Urgent evaluation and management are required, because the blood supply to the testis is compromised, which results in irreversible ischemic damage to the testis; condition may occur in utero (Lissauer, 2015; Mangurten et al., 2015).
Musculoskeletal System		
Arachnodactyly	Unusually long, spiderlike digits.	Characteristic of, but not universally present in, Marfan syndrome and homocystinuria (Parikh & Mitchell, 2015).
Arthrogryposis	Persistent flexure or contracture of one or more joints.	May be associated with oligohydramnios or an underlying neuromuscular disorder (Parikh & Mitchell, 2015).
Brachydactyly	Shortening of one or more digits as a result of abnormal development of phalanges, metacarpals, or metatarsals.	Benign trait if an isolated finding; may be a component of skeletal dysplasias (achondroplasia) and syndromes (trisomy 21; Parikh & Mitchell, 2015).
Calcaneus foot	Abduction of the forefoot with the heel in valgus position (turned outward).	Associated with external tibial torsion; often caused by in utero positioning.

(*continued*)

TABLE 4.12

ABNORMALITIES AND VARIATIONS FOUND ON PHYSICAL EXAMINATION OF NEWBORNS AND INFANTS (*continued*)

Finding	Definition/Description	Comments
Camptodactyly	Congenital flexion deformity of the finger; bent finger.	Usually involves the little finger; can be a minor variant, familial trait, or part of a syndrome (Parikh & Mitchell, 2015).
Clinodactyly	Lateral angulation deformity of a finger with either radial or ulnar deviation.	Usually involves the little finger; may be a benign finding if occurring alone but can be associated with congenital syndromes (Parikh & Mitchell, 2015).
Crepitus	Crackling sensation produced by the presence of air in tissues (subcutaneous emphysema) or the movement of bone fragments (clavicular fracture).	
Genu recurvatum	Abnormal hyperextensibility of the knee allowing the knee to bend backward.	May be due to trauma, prolonged intrauterine pressure, or general joint laxity. May be a feature of other disorders (Ehlers-Danlos, Marfan syndromes; Son-Hing & Thompson, 2015; Walker, 2018).
Kyphosis	Round shoulder deformity; forward bending of the spine. Caused by congenital failure of formation of all or part of the vertebral body, with preservation of the posterior elements and failure of the anterior segmentation of the spine.	Severe deformities may be apparent at birth; less severe abnormalities may not appear until several years later; a progressive deformity can result in paraplegia (Parikh & Mitchell, 2015; Son-Hing & Thompson, 2015).
Lordosis	Exaggeration of the normal curvature in the cervical and lumbar spine.	Caused by a bony abnormality of the spine (Bennett & Meier, 2019).
Lymphedema	Puffiness of the dorsum of the hands or feet.	Characteristic of Noonan's or Turner's syndrome (Parikh & Mitchell, 2015).
Meningocele	Saclike protrusion of the spinal meninges through a congenital defect in the spinal column.	Herniated cyst is filled with cerebrospinal fluid but does not contain neural tissue; affected infants usually do not show neurologic deficits (Robinson & Cohen, 2015b).
Metatarsus valgus	Congenital deformity of the foot in which the forepart rotates outward away from the midline and the heel remains straight.	Fixed deformity of the foot, which cannot be brought into neutral position; compare with metatarsus adductus, a functional deformity in which the foot can be brought into neutral position (Grover, 2000b; Son-Hing & Thompson, 2015).
Metatarsus varus	Congenital bony abnormality of the foot in which the forepart rotates inward toward the midline and the heel remains straight.	Fixed deformity; the foot cannot be brought into neutral position. Compare with metatarsus adductus, a functional deformity in which the foot can be brought into neutral position (Son-Hing & Thompson, 2015).
Myelomeningocele	Defect identical to meningocele but with associated abnormalities in the structure and position of the spinal cord.	Affected infants usually show neurologic deficits below the level of the abnormality (Robinson & Cohen, 2015b).
Polydactyly	Presence of more than the normal number of digits; there may be a complete extra digit (preaxial) that is normal in appearance, or a skin tag (postaxial).	May be an isolated finding, inherited as an autosomal dominant trait, or may occur in a variety of syndromes (trisomy 13, Meckel–Gruber syndrome; Cooperman & Thompson, 2011; Parikh & Mitchell, 2015; Son-Hing & Thompson, 2015).
Rachischisis	Congenital fissure of the spinal cord in which the incompletely folded cord is splayed apart and exposed along the back.	Caused by incomplete neurulation; often accompanied by anencephaly (Fletcher, 1998; Gressens & Huppi, 2015).

(*continued*)

TABLE 4.12

ABNORMALITIES AND VARIATIONS FOUND ON PHYSICAL EXAMINATION OF NEWBORNS AND INFANTS (*continued*)

Finding	Definition/Description	Comments
Rocker bottom feet	Deformity of the foot in which the arch is disrupted, giving a rounded appearance (rocker bottom) to the sole.	Usually seen in conjunction with congenital syndromes (trisomies 13 and 18; Parikh & Mitchell, 2015; Son-Hing & Thompson, 2015).
Scoliosis	Failure of formation or segmentation of the vertebrae; manifests as lateral (side to side) curvature of the spine.	May be congenital or acquired; may occur as part of another condition or may be idiopathic (Son-Hing & Thompson, 2015).
Simian crease	Single transverse line in the palm.	May be benign, but when accompanied by other dysmorphic features (e.g., incurving fifth finger, epicanthal folds, low-set thumb), it may be a sign of trisomy 21 (Parikh & Mitchell, 2015).
Spinal dimple, dermal sinus	Pit or depression that occurs along the midline of the back, often at the base of the spinal cord in the lumbosacral area; may be accompanied by tufts of hair.	May be a benign finding, especially if the base of the defect can be visualized; however, defect can extend into the spinal cord, representing a neural tube defect and tethered spinal cord (Heaberlin, 2019; Liu & Thompson, 2015).
Syndactyly	Fusion of two or more digits; may involve only soft tissue (simple) or may include bone or cartilage (complex).	May occur as an isolated defect or as part of a syndrome (e.g., Cornelia de Lange's, Smith-Lemli-Opitz; Son-Hing & Thompson, 2015).
Talipes equinovarus	Clubfoot; congenital deformity of the foot and lower leg marked by adduction of the forefoot (turned inward and pointed medially), varus position of the heel (turned inward), and downward pointing of the toes.	May be congenital (isolated deformity), teratologic (associated with underlying neuromuscular disorder), or positional (normal foot held in equinovarus position in utero; Son-Hing & Thompson, 2015).
Tibial torsion	Abnormal rotation of the feet while the knees are pointing forward; may be internal (toes in) or external (toes out).	Often caused by in utero positioning; resolves spontaneously (Son-Hing & Thompson, 2015).
Torticollis	Shortening of the sternocleidomastoid muscle, resulting in head tilt toward the affected muscle and chin rotation toward the unaffected muscle; a palpable mass may appear during the first few weeks of life.	May be due to birth trauma, intrauterine malposition, muscle fibrosis, venous abnormalities in the muscle, or congenital cervical vertebral abnormalities (Liu & Thompson, 2015).
Neurologic Examination		
Brachial plexus injuries	Peripheral damage to the network of spinal nerves supplying the arm, forearm, and hand.	Multifactorial etiology; interaction between characteristics of the brachial plexus, maternal and fetal risk factors, and birth trauma (Liu & Thompson, 2015).
	Erb–Duchenne palsy (upper arm paralysis): Arm is adducted and internally rotated, with elbow extension, flexion of the wrist, and pronation of the forearm. The arm falls to the side of the body when passively abducted, and the Moro reflex is absent on the affected side but the grasp is intact.	Arises from injury to the fifth and sixth cervical roots; most common brachial plexus injury (Liu & Thompson, 2015; Mangurten et al., 2015).
	Klumpke palsy (lower arm paralysis): Hand is paralyzed, and voluntary movement of the wrist and grasp reflex *are* absent.	Rare; results from injury to the eighth cervical and first thoracic roots; usually Horner's syndrome (ptosis, miosis, and enophthalmos) is present on the affected side; delayed pigmentation of the iris may be seen (Liu & Thompson, 2015; Mangurten et al., 2015).

(*continued*)

TABLE 4.12

ABNORMALITIES AND VARIATIONS FOUND ON PHYSICAL EXAMINATION OF NEWBORNS AND INFANTS (*continued*)

Finding	Definition/Description	Comments
	Paralysis of the entire arm: Arm is completely motionless, flaccid, and powerless and hangs limply; all reflexes are absent, and sensory deficit may extend to the shoulder.	Liu & Thompson (2015).
Facial nerve palsy	Facial weakness or paralysis arising from compression of the seventh cranial nerve, caused by intrauterine position or forceps delivery; characterized by asymmetry of facial movement (most evident on crying), ptosis, and unequal nasolabial folds.	Mangurten et al. (2015).
Phrenic nerve injury	Cause of respiratory distress secondary to paralysis of the diaphragm; arises from upper brachial plexus injury.	Rarely occurs as an isolated phenomenon; accompanies signs and symptoms of Erb–Duchenne palsy (Mangurten et al., 2015).

CPAP, continuous positive airway pressure; GA, gestational age; GI, gastrointestinal; GU, genitourinary; LBW, low birth weight; OFC, occipitofrontal circumference.

HEALTH MAINTENANCE IN THE FIRST YEAR OF LIFE

The goal of health maintenance, or primary care, is to provide consistent preventive healthcare for the infant and education for the parents. In addition to the basic surveillance provided for all infants, high-risk infants have other needs that must be addressed. Primary care for these infants often requires a multidisciplinary approach, and the healthcare provider is responsible for coordinating medical, developmental, and social services. Because high-risk infants face the possibility of developmental delays, neurologic sequelae, and nutritional deficits, follow-up must include formal developmental, neurologic, and nutritional assessments in addition to routine screening tests. The healthcare provider may need to schedule longer and more frequent visits to evaluate the infant adequately and to assess the family's adjustment to caring for the child. The healthcare provider also is responsible for giving the parents comprehensive anticipatory guidance (Santos & Smith, 2014).

There are published guidelines for health supervision (Bellflower, 2017; Dunn, 2016; Hagan, Shaw, & Duncan, 2017). These guidelines indicate the elements that can be included in office visits for patients from birth to 18 years of age. They are intended to be used for those infants and children whose health needs are considered to be within the normal range. Although the guidelines were intended to be flexible and easily modified for follow-up of high-risk infants, there are specific resources available for chronic and disabling conditions (Allen, 2010; Stewart & Joselow, 2012). The reader is encouraged to consult these resources for assistance in planning health maintenance both for normal infants and those with special needs. In the current healthcare arena, information is updated rapidly and readers are encouraged to use the most recently updated guidelines.

Immunizations

Both the Centers for Disease Control and Prevention (CDC) and the AAP have published recommendations for routine childhood immunization through the first 18 years of age. The latest recommendations can be accessed at the following websites: https://www.cdc.gov/vaccines/schedules/downloads/child/0-18yrs-child-combined-schedule.pdf and https://pediatrics.aappublications.org/content/143/3/e20190065

It is beneficial to routinely check these websites for the most up-to-date information about immunizations rather than relying on journals or textbooks, which may not have been recently updated.

HEALTH MAINTENANCE FOR HIGH-RISK INFANTS IN THE FIRST YEAR OF LIFE

History

It is important for the primary care provider to review the infant's medical history, including a complete family history and the record of the hospital course (Table 4.13). In addition to providing routine healthcare maintenance and anticipatory guidance to the parents, the primary care provider must monitor the status of associated medical conditions and developmental sequelae.

Growth and Nutrition

Weight, length/height, and OFC are measured and plotted on the appropriate graphs. Expected increases in these parameters are summarized in Table 4.14. The parameters for premature infants must be corrected for preterm birth. Adjustments generally are made until 2 to 2½ years of age. Premature infants frequently show accelerated ("catch-up") growth, which first manifests in the head circumference. This may begin as early as 36 weeks postconceptional age or as late as 8 months adjusted age (Sifuentes, 2000). Increases in the OFC of more than 2 cm/week are worrisome and should be investigated, because they may signify a pathologic process (hydrocephalus) rather than catch-up growth (Kelly, 2010).

Weight gain is evaluated in grams per day. Many high-risk infants are placed on special diets (24 calories/oz) or feeding regimens (feedings every 2 hours or continuous feedings). It is important to review the necessity of continuing or modifying the feeding plan according to the adequacy of growth. The need

TABLE 4.13

RECORDED ELEMENTS OF THE HISTORY, MEDICAL COURSE, AND CURRENT NEEDS FOR NEONATES

Component	Elements
History	Prenatal and perinatal course Hospital course: Birth weight, gestation Illnesses, surgical procedures Radiographic studies Discharge examination Weight, head circumference, length
Nutrition information	Current diet and feeding schedule Feeding problems: GE reflux, feeding intolerance Dietary supplements: Vitamins, minerals, human milk fortifier Current deficiencies: Osteopenia/rickets, anemia
Medications	Doses Serum levels Oxygen requirements
Immunizations	Immunizations given in the hospital Respiratory syncytial virus prophylaxis
Laboratory data	Most recent values: Hemoglobin, hematocrit Bilirubin Pending laboratory studies Need for further testing Newborn screening results
Current problems and complications	Retinopathy of prematurity, ophthalmologic problems (e.g., strabismus) Hearing deficits Bronchopulmonary dysplasia/chronic lung problems GE reflux Intraventricular hemorrhage Developmental deficits Other

GE, gastroesophageal.

Source: Data from Santos, L. S., & Smith, L. A. (2014). Well-child care for the preterm infant. In C. D. Berkowitz (Ed.), *Berkowitz's pediatrics: A primary care approach* (e Version) (5th ed., Chapter 40). Philadelphia, PA: American Academy of Pediatrics. Retrieved from http://ebooks.aappublications.org/content/9781581108514/9781581108514

for dietary supplements (vitamins, minerals, human milk fortifier), medications (ranitidine, metoclopramide), and biochemical monitoring (e.g., for rickets or osteopenia) should also be addressed.

Physical Examination

A complete physical examination should be performed at each visit. Depending on the infant's history and needs, special attention may be required in certain areas, which are listed in Table 4.15.

TABLE 4.14

EXPECTED INCREASES IN WEIGHT, LENGTH/HEIGHT, AND HEAD CIRCUMFERENCE IN THE FIRST YEAR OF LIFE

Parameter	Age (months)	Expected Increase
Weight	Birth to 3	25–35 g/day
	3–6	12–21 g/day
	6–12	10–13 g/day
Length/height	Birth to 12	25 cm/year
OFC	Birth to 3	2 cm/months
	4–6	1 cm/months
	7–12	0.5 cm/months

OFC, occipitofrontal circumference.

Sources: Data from Grover, G. (2000). Nutritional needs. In C. D. Berkowitz (Ed.), *Pediatrics: A primary care approach* (2nd ed.). Philadelphia, PA: Saunders; Duffy, L. V. (2010). Hydrocephalus. In P. J. Allen, J. A. Vessey, & N. A. Schopira (Eds.), *Primary care of the child with a chronic condition* (5th ed., pp. 564–561). St. Louis, MO: Mosby.

TABLE 4.15

MONITORING FOR SUBSEQUENT CONDITIONS IN HIGH-RISK INFANTS

System	Condition	Comments
Ocular	ROP, strabismus, visual abnormalities	
Oropharyngeal	Palatal groove, high-arched palate, abnormal tooth formation	May develop secondary to intubation or may be due to congenital abnormalities
	Discolored teeth	Caused by high bilirubin levels
Thoracic/ respiratory	Retractions, wheezing, stridor, chest scars	Sequelae of chronic lung disease. Caused by chest tube placement
Cardiovascular	Hypertension	Blood pressure monitoring is especially important for an infant who had umbilical artery catheters in place
Abdominal	Hypoplastic umbilicus	Use of umbilical catheters and suturing frequently are the cause of this condition

(*continued*)

TABLE 4.15

MONITORING FOR SUBSEQUENT CONDITIONS IN HIGH-RISK INFANTS (*continued*)

System	Condition	Comments
Genitourinary	Hernias Cryptorchidism	Increased risk in preterm babies
Extremities	Developmental hip dysplasia Scars on heels or extremities	Sequelae of blood sampling, placement of IV lines, or extravasation of IV fluid
Neuromuscular	Abnormal tone, asymmetric movements and reflexes, persistence of primitive reflexes and fisting, sustained clonus, scissoring, poor suck-swallow coordination	Abnormalities must be identified as soon as possible and the patient and family referred to appropriate intervention services

IV, intravenous; ROP, retinopathy of prematurity.

Sources: Data from Allen, P. J. (2010). The primary care provider and children with chronic conditions. In P. J. Allen, J. Vessey, & N. Shapiro (Eds.), *Primary care of the child with a chronic condition* (5th ed., pp. 3–21). St. Louis, MO: Elsevier. Santos, L. S., & Smith, L. A. (2014). Well-child care for the preterm infant. In C. D. Berkowitz (Ed.), *Berkowitz's pediatrics: A primary care approach* (e Version) (5th ed., Chapter 40). Philadelphia, PA: American Academy of Pediatrics. Retrieved from http://ebooks.aappublications.org/content/9781581108514/9781581108514

Laboratory Tests and Monitoring Examinations

All standard screening tests required for healthy infants should be performed according to AAP recommendations. Other tests may be necessary for high-risk infants, such as periodic electrolyte determinations for babies receiving diuretics. Consideration should be given to measuring serum levels for such drugs as anticonvulsants, methylxanthines, and digoxin.

Repeat ophthalmologic examinations may be required to evaluate the extent and progression or regression of retinopathy of prematurity (ROP). Further follow-up may be indicated, because some infants are at risk for strabismus, myopia, amblyopia, glaucoma, and other visual deficits. The infant may need serial auditory evaluations (brainstem auditory evoked response [BAER] behavioral audiograms) and other studies, such as electroencephalography, electrocardiography, echocardiography, radiography, pneumography, and neuroradiologic imaging (CT or MRI). Infants receiving supplemental oxygen often benefit from periodic pulse oximetry (Kelly, 2010; Santos & Smith, 2014).

Immunizations

Vaccines are administered according to chronologic (postnatal) age, not GA. The standard doses and intervals are followed, as recommended by the AAP and/or CDC (see Immunizations section). Former premature infants have adequate serologic responses to immunizations without increased incidence of untoward effects. There is benefit derived from respiratory syncytial virus (RSV) prophylaxis for high-risk infants, especially premature infants with a history of respiratory distress syndrome (RDS) or RDS/BPD (RDS with bronchopulmonary dysplasia).

Box 4.1

CHARACTERISTICS OF VCS

- Exaggerated separation anxiety (both infant and parent)
- Sleep difficulties
- Overprotectiveness
- Overindulgence
- Lack of appropriate discipline
- Excessive parental preoccupation with infant's health

Psychosocial Needs

Families of high-risk infants require a great deal of support and anticipatory guidance. Healthcare providers must seek to understand parental expectations and legitimize their fears while providing support and encouragement. Parents should be given consistent, honest information and realistic appraisals of their infant's status and prognosis.

NICU graduates may be at risk for vulnerable child syndrome (VCS; Box 4.1). Because parents continue to perceive their child as vulnerable and fragile, abnormal parent–infant interactions develop. By assessing for early, subtle signs, healthcare providers may prevent progression of the disorder.

SUMMARY

The comprehensive history and physical assessment create the framework for identifying problems and planning interventions. Assessment allows the nurse to gather information and to evaluate and integrate that information as care of the newborn proceeds. Although careful attention to the obvious is important, subtle findings detected by an experienced practitioner also may play a crucial role in the continuing care of the infant and family.

CASE STUDY

■ **Identification of Patient Problem.** You are assessing a full-term female infant who was born 15 minutes previously via vaginal delivery. You note a firm but fluctuant cranial mass with ill-defined borders swelling across the suture lines to the ear and neck. The pinna appears to be protuberant.

■ **Assessment: History and Physical Examination.** Obtain detailed history to include:

- Maternal medications used during pregnancy (aspirin, ibuprofen, phenytoin)
- History of placental insufficiency or fetal asphyxia during delivery
- Length of time spent pushing
- If delivery was vacuum assisted, number of attempts and length of application
- Presentation of fetus at delivery

- Infant's Apgar scores
- History of previous child with clotting or bleeding disorder
- Family history of bleeding or clotting disorders
- Detailed examination (to be performed on open warmer): Observe general appearance of infant including color of skin and mucous membranes, overall perfusion, size and symmetry of head and face, obvious deformities or evidence of birth trauma
- Monitor vital signs (VS)

Assess state of alertness, tone, resting posture/position, and cry

- Note any arching or posturing with movement

Head

- Observe general appearance, size, and movement of head and neck
- Observe shape and symmetry of head, neck, and pinna bilaterally
- Inspect and palpate sutures and fontanelles
- Measure head circumference
- Observe hair growth patterns and check for signs of birth trauma or other anomalies
- Auscultate fontanelles

Face

- Observe for symmetrical movement of facial features
- Assess eyes, pupillary response to light, red reflex, and blink reflex in response to light
- Inspect for facial, head, and neck edema, and ecchymosis
- Assess gag, suck/rooting reflex, palate, color of mucous membranes, suck/swallow coordination, tongue, midline, moves freely, color, proportional size
- Observe for facial palsy

Ears

- Assess for any drainage or bleeding from the ear canals
- Inspect shape, placement, swelling, and position of ears
- Inspect ears for lesions, cysts, nodules
- Inspect nose: appearance, patency of nares

Neck

- Observe appearance, noting any abnormalities such as short, redundant skin, webbing
- Assess clavicles

Chest

- Assess color and perfusion prior to starting examination and note any changes throughout examination
- Palpate quality of pulses and compare upper to lower
- Observe for active precordium
- Assess capillary refill
- Auscultate lung sounds, noting any retractions, grunting, flaring, asymmetrical chest movement, or aeration
- Auscultate chest for murmurs, clicks, and rubs; PMI
- Assess for placement of breasts/nipples, presence of breast tissue, symmetry

Abdomen

- Observe color and size, shape, and symmetry of abdomen
- Auscultate abdomen for bowel sounds
- Palpate for loops, noting any tenderness and guarding with examination
- Palpate for hepatosplenomegaly

Genitourinary

- Inspect external genitalia and inguinal area/suprapubic area
- Inspect labia, clitoris, urethral meatus, and any bleeding or discharge
- Inspect for any discoloration/bruising or other signs of birth trauma
- Assess anus for patency and placement

Musculoskeletal

- Observe for spontaneous, symmetrical movement in all four limbs
- Inspect entire body for ecchymosis and petechiae or other signs of bleeding with careful documentation (mark borders if necessary)

Neurologic

- Assess reflexes: tonic neck reflex, Moro reflex, grasp reflex, Babinski reflex, and trunk incurvation

Differential Diagnosis

- Caput succedaneum, cephalohematoma, skull fracture, subgaleal hematoma

Diagnostic Tests

- Continuous monitoring: heart rate, respiratory rate, blood pressure, and pulse oximetry
- Blood gas to assess for metabolic acidosis
- Hematocrit, platelets, clotting factors, to assess for blood loss and/or coagulopathy
- Liver function studies, blood glucose level
- Skull radiograph to assess for skull fracture
- Depending on the results of the neurologic examination, a head CT may be necessary

Working Diagnosis

- Subgaleal hemorrhage

Development of Management Plan

- Admit to NICU for close observation
- Monitor VS closely and continuously (HR, RR, BP); pulse oximetry, observing closely for signs of hypovolemic shock (tachycardia, hypotension, respiratory distress)
- Monitor neurologic VS closely for possible deterioration in level of consciousness
- Monitor intake and output strictly

Blood work to be done:

- Blood gas (for baseline respiratory function)
- Complete blood count (for baseline hematocrit)
- Coagulation factors (for potential indication of massive bleeding and coagulopathy)
- Bilirubin level (for baseline: during resolution the breakdown of the blood may cause hyperbilirubinemia requiring treatment; thus, levels of bilirubin need to be followed closely as well)
- Blood urea nitrogen and creatinine (for baseline of kidney function and hydration)

- Keep the patient NPO for now
- Provide maintenance IV solution
- Blood products or normal saline (NS) boluses can be given as required for replacement of blood volume

Meet with parents: Careful preparation of the parents for the acute side effects and sequelae of subgaleal hemorrhage is important. Parents should be warned of the possibility of swelling and discoloration of the face, head, and neck. They should also know that spontaneous resolution usually occurs within 2 to 3 weeks and some infants require close long-term follow-up for sequelae.

■ Implementation and Evaluation of Effectiveness

Implement the previously noted plan with continuous monitoring for deterioration of infant's cardiovascular or neurologic status.

EVIDENCE-BASED PRACTICE BOX

Assessment

Although the 10-point Apgar score has been used to evaluate the physical condition of newly born infants since it was proposed by Virginia Apgar in 1952, its value has become controversial due to attempts to use it as a predictor of neurologic outcome. Casey, McIntire, and Leveno (2001) studied whether the Apgar scoring system remains relevant as a prognosticator of survival during the neonatal period, an intent for which it was originally developed. Based on their analysis, these investigators concluded that the Apgar system continues to be an important tool in the prediction of neonatal outcome.

However, more recently opposing evidence has emerged. Even a 5-minutes score of 0 to 3, although possibly a result of hypoxia, is limited as an indicator of the severity of the problem and in and of itself correlates poorly with future neurologic outcome (Stanley, 1994; Weiner, Zaichkin, & Kattwinkel, 2016). The prevailing opinion is that the Apgar score should not be used in isolation to predict morbidity or mortality for any particular neonate, but is intended to convey information about the newborn's response to resuscitation (Goldsmith, 2015).

References

Casey, B. M., McIntire, D. D., & Leveno, K. J. (2001). The continuing value of the Apgar score for the assessment of newborn infants. *New England Journal of Medicine, 344*(7), 467–471. doi:10.1056/NEJM200102153440701

Goldsmith, J. (2015). Overview and initial management of delivery room resuscitation In R. J. Martin, A. A. Fanaroff, & M. C. Walsh (Eds.), *Fanaroff & Martin's neonatal-perinatal medicine: Diseases of the fetus and infant* (10th ed., pp. 460–470). St. Louis, MO: Elsevier.

Stanley, F. J. (1994). Cerebral palsy trends: Implications for perinatal care. *Acta Obstetricia et Gynecologica Scandinavica (Copenhagen), 73*, 5–9. doi:10.3109/00016349409013384

Weiner, G. M., Zaichkin, J., & Kattwinkel, J. (Eds.). (2016). *Textbook of neonatal resuscitation* (7th ed.). Elk Grove, IL: American Academy of Pediatrics & American Heart Association.

ONLINE RESOURCES

ballardscore. (2007, February 7). *New Ballard score–Chapter 2* [Video file]. Retrieved from https://www.youtube.com/results?search_query=ballard+score

ballardscore. (2007, February 8). *New Ballard score–Chapter 3* [Video file]. Retrieved from https://www.youtube.com/results?search_query=ballard+score

MDforAll. (2010, August 25). *Pediatrics–Infant* [Vidoe file]. Retrieved from http://www.youtube.com/watch?v=8gnO4Py0_08

medicalgallery. (2010, August 1). *Medical gallery–Loyola neonatal exam part 1–Pediatrics.flv* [Video file]. Retrieved from http://www.youtube.com/watch?v=yAWEWfwyWBo

Physical assessment of the newborn. (n.d.). Retrieved from http://www.duq.edu/academics/schools/nursing/newborn-assessment

REFERENCES

Abdulhayoglu, E. (2017). Birth trauma. In E. C. Eichenwald, A. R. Hansen, C. Martin, & A. R. Stark (Eds.), *Cloherty & Stark's manual of neonatal care* (8th ed., pp. 64–75). Philadelphia, PA: Lippincott Williams & Wilkins.

Allen, P. J. (2010). The primary care provider and children with chronic conditions. In P. J. Allen, J. Vessey, & N. Shapiro (Eds.), *Primary care of the child with a chronic condition* (5th ed., pp. 3–21). St. Louis, MO: Elsevier.

Al Remeithi, S., & Wherrett, K. (2015). Disorders of sex development. In R. J. Martin, A. A. Fanaroff, & M. C. Walsh (Eds.), *Fanaroff & Martin's neonatal-perinatal medicine: Diseases of the fetus and infant* (10th ed., pp. 1516–1552). St. Louis, MO: Elsevier.

Als, H., & Butler, S. (2011). Neurobehavioral development of the preterm infant. In R. J. Martin, A. A. Fanaroff, & M. C. Walsh (Eds.), *Fanaroff & Martin's neonatal-perinatal medicine: Diseases of the fetus and infant* (9th ed., pp. 1057–1074). St. Louis, MO: Mosby.

American Academy of Pediatrics Committee on Fetus and Newborn & American College of Obstetricians and Gynecologists Committee on Obstetric Practice. (2015). The Apgar score. *Pediatrics, 136*(4) 819–822. doi:10.1542/peds.2015-2651

Apgar, V. A. (1953). A proposal for a new method of evaluation of the newborn infant. *Current Research in Anesthesiology and Analgesia, 32*, 260–267. doi:10.1213/00000539-195301000-00041

Ball, J. W., Dains, J. E., Flynn, J. A., Solomon, B. S., & Stewart, R. W. (2015). *Seidel's guide to physical examination* (8th ed.). St. Louis, MO: Elsevier.

Ballard, J. L., Khoury, J. C., Wedig, K., Wang, L., Eilers-Walsman, B. L., & Lipp, R. (1991). New Ballard score, expanded to include extremely premature infants. *Journal of Pediatrics, 119*, 417–423. doi:10.1016/S0022-3476(05)82056-6

Battaglia, F. C., & Lubchenco, L. O. (1967). A practical classification of newborn infants by weight and gestational age. *Journal of Pediatrics, 71*, 159–163. doi:10.1016/S0022-3476(67)80066-0

Bauer-Huang, S., & Doherty, D. (2018). Congenital malformations of the central nervous system. In C. A. Gleason & S. E. Juul (Eds.), *Avery's diseases of the newborn* (10th ed., pp. 857–879). Philadelphia, PA: Saunders.

Bellflower, B. (2017). Health promotion: Newborn through the first year of life. In S. Bellini & M. J. Beaulieu (Eds.), *Neonatal advanced*

practice nursing. A case-based learning approach (pp. 387–411). New York, NY: Springer Publishing Company.

Bennett, M., & Meier, S. (2019). Assessment of the dysmorphic infant. In E. P. Tappero & M. E. Honeyfield (Eds.), *Physical assessment of the newborn* (6th ed., pp. 219–238). New York, NY: Springer Publishing Company.

Broderick, G. A. (2016). Priapism. In A. J. Wein, L. R. Kavoussi, A. W. Partin, & C. A. Peters (Eds.), *Campbell-Walsh urology* (11th ed., pp. 669–691). Philadelphia, PA: Elsevier.

Burton-Mota, J. (2014). Nutritional needs. In C. D. Berkowitz (Ed.), *Berkowitz's pediatrics: A primary care approach* [e Version] (5th ed., Chapter 25). Philadelphia, PA: American Academy of Pediatrics. Retrieved from http://ebooks.aappublications.org/content/9781581108514/9781581108514

Calkins, K. L., & Devaskar, S. U. (2015). Intrauterine growth restriction. In R. J. Martin, A. A. Fanaroff, & M. C. Walsh (Eds.), *Fanaroff & Martin's neonatal-perinatal medicine: Diseases of the fetus and infant* (10th ed., pp. 227–235). St. Louis, MO: Elsevier.

Carley, A., & Duderstadt, K. (2019). Newborn assessment. In K. G. Duderstadt (Ed.), *Pediatric physical examination. An illustrated handbook* (3rd ed., pp. 67–88). St. Louis, MO: Elsevier.

Cavaliere, T.A. (2016). From fetus to neonate: A sensational journey. *Newborn and Infant Nursing Reviews, 16*(2), 43–47. doi:10.1053/j.nainr.2016.03.004

Cavaliere, T. A. (2019). Genitourinary assessment. In E. P. Tappero & M. E. Honeyfield (Eds.), *Physical assessment of the newborn* (6th ed., pp. 121–138). New York, NY: Springer Publishing Company.

Cavaliere, T. A., & Sansoucie, D. A. (2014). Assessment of the newborn and infant. In C. Kenner & L. W. Lott (Eds.), *Comprehensive neonatal nursing: A physiologic perspective* (4th ed., pp. 71–112). New York, NY: Springer Publishing Company.

Centers for Disease Control and Prevention. (n.d.) *Information about early hearing detection and intervention (EHDI) state programs*. Retrieved from https://www.cdc.gov/ncbddd/hearingloss/ehdi-programs.html

Cooperman, D. R., & Thompson, G. H. (2011). Neonatal orthopedics. In R. J. Martin, A. A. Fanaroff, & M. C. Walsh (Eds.), *Fanaroff & Martin's neonatal-perinatal medicine: Diseases of the fetus and infant* (9th ed., pp. 1771–1801). St. Louis, MO: Mosby.

Desmond, M. M., Rudolph, A. J., & Phitaksphraiwan, P. (1966). The transitional care nursery. A mechanism for preventive medicine in the newborn. *Pediatric Clinics of North America, 13*(3), 651–668. doi:10.1016/S0031-3955(16)31875-2

Duderstadt, K. (2019). Assessment parameters. In K. G. Duderstadt (Ed.), *Pediatric physical examination. An illustrated handbook* (3rd ed., pp. 9–21). St. Louis, MO: Elsevier.

Duffy, L. V. (2010). Hydrocephalus. In P. J. Allen, J. A. Vessey, & N. A. Schapiro (Eds.), *Primary care of the child with a chronic condition* (5th ed., pp. 564–561). St. Louis, MO: Mosby.

Dunn, A. M. (2016). Child and family health assessment. In C. E. Burns, A. M. Dunn, M. A. Brady, N. B. Starr, C. G. Blosser, & D. L Garzon (Eds.), *Pediatric primary care* (6th ed., pp. 10–32). St. Louis, MO: Saunders.

Earley, A., Fayers, P., Ng, S., Shinebourne, E. A., & de Sweit, M. (1980). Blood pressure in the first six weeks of life. *Archives of Disease in Childhood, 55*, 755–757. doi:10.1136/adc.55.10.755

Elder, J. S. (2016). Disorders and anomalies of the scrotal contents. In R. M. Kleigman, B. M. D. Stanton, J. St Geme, & N. Schor (Eds.), *Nelson textbook of pediatrics* (20th ed., pp. 2592–2598). Philadelphia, PA: Elsevier.

Engel, J. (2006). *Pocket guide to pediatric assessment* (5th ed.). St. Louis, MO: Mosby.

Ezenwa, B. N., & Ezeaka, V. C. (2018). Is CANSCORE a good indicator of fetal malnutrition in preterm newborns? *Alexandria Journal of Medicine, 54*, 57–61. doi:10.1016/j.ajme.2017.01.004

Fanaroff, A. A., & Wright, E. (1990). Profiles of mean arterial blood pressure (MAP) for infants weighing 500–1500 grams. *Pediatric Research, 27*, 205A.

Felner, J. M. (1990). An overview of the cardiovascular system. In H. K. Walker, W. D. Hall, & J. W. Hurst (Eds.), *Clinical methods: The history, physical, & laboratory examinations* (3rd ed.). Atlanta, GA: Emory University School of Medicine.

Fletcher, M. A. (1998). *Physical diagnosis in neonatology*. Philadelphia, PA: Lippincott-Raven.

Fraser, D. (2019). Chest and lungs assessment. In E. P. Tappero & M. E. Honeyfield (Eds.), *Physical assessment of the newborn* (6th ed., pp. 79–91). New York, NY: Springer Publishing Company.

Furdon, S. A., & Clark, D. A. (2003). Scalp hair characteristics in the newborn. *Advances in Neonatal Care, 3*(6), 286–298. doi:10.1016/j.adnc.2003.09.005

Gardner, S. L., & Hernandez, J. A. (2016). Initial nursery care. In S. L. Gardner, B. S. Carter, M. I. Enzman-Hines, & J. A. Hernandez (Eds.), *Merenstein & Gardner's handbook of neonatal intensive care* (8th ed., pp. 71–104). St. Louis, MO: Elsevier.

Goldsmith, J. (2015). Overview and initial management of delivery room resuscitation. In R. J. Martin, A. A. Fanaroff, & M. C. Walsh (Eds.), *Fanaroff & Martin's neonatal-perinatal medicine: Diseases of the fetus and infant* (10th ed., pp. 460–470). St. Louis, MO: Elsevier.

Gomella, T. L. (2013). Newborn physical examination. In T. L. Gomella, M. D. Cunningham, & F. G. Eyal (Eds.), *Neonatology: Management, procedures, on all problems, diseases, & drugs* (7th ed., pp. 43–64). New York, NY: McGraw-Hill.

Goodwin, M. (2019). Abdomen assessment. In E. P. Tappero & M. E. Honeyfield (Eds.), *Physical assessment of the newborn* (6th ed., pp. 111–120). New York, NY: Springer Publishing Company.

Gressens, P., & Huppi, P. (2015). Normal and abnormal brain development. In R. J. Martin, A. A. Fanaroff, & M. C. Walsh (Eds.), *Fanaroff & Martin's neonatal-perinatal medicine: Diseases of the fetus and infant* (10th ed., pp. 836–865). St. Louis, MO: Mosby.

Grover, G. (2000a). Nutritional needs. In C. D. Berkowitz (Ed.), *Pediatrics: A primary care approach* (2nd ed.). Philadelphia, PA: Saunders.

Grover, G. (2000b). Rotational problems of the lower extremities: Intoeing and out-toeing. In C. D. Berkowitz (Ed.), *Pediatrics: A primary care approach* (2nd ed). Philadelphia, PA: Saunders.

Hagan, J. F., Shaw, J. S., & Duncan, P. (Eds.). (2017). *Bright futures. Guidelines for health supervision of infants, children, and adolescents* (4th ed.). Elk Grove, IL: American Academy of Pediatrics.

Heaberlin, P. D. (2019). Neurologic assessment. In E. P. Tappero & M. E. Honeyfield (Eds.), *Physical assessment of the newborn* (6th ed., pp. 167–192.). New York, NY: Springer Publishing Company.

Hegyi, T., Carbone, M. T., Anwar, M., Ostfeld, B., Hiatt, M., Koons, A., . . . Paneth, N. (1994). Blood pressure ranges in premature infants. I. The first hours of life. *Journal of Pediatrics, 124*, 627–633. doi:10.1016/S0022-3476(05)83146-4

Hoath, S. B., & Narendran, V. (2015). The skin. In R. J. Martin, A. A. Fanaroff, & M. C. Walsh (Eds.), *Fanaroff & Martin's neonatal-perinatal medicine: Diseases of the fetus and infant* (10th ed., pp. 1702–1732). St. Louis, MO: Elsevier.

Honeyfield, M. E. (2019). Principles of physical assessment. In E. P. Tappero & M. E. Honeyfield (Eds.), *Physical assessment of the newborn* (6th ed., pp. 1–8). New York, NY: Springer Publishing Company.

Johnson, L. (2017). Assessment of the newborn history and physical examination of the newborn. In E. C. Eichenwald, A. R. Hansen, C. R. Martin, & A. R. Stark (Eds.), *Cloherty and Stark's manual of neonatal care* (8th ed., pp. 94–105). Philadelphia, PA: Lippincott Williams & Wilkins.

Johnson, P. J. (2019). Head, eyes, ears, nose, mouth, and neck assessment. In E. P. Tappero & M. E. Honeyfield (Eds.), *Physical assessment of the newborn* (6th ed., pp. 61–78). New York, NY: Springer Publishing Company.

Karfer, M. (2016). Management of abnormalities of the genitalia in girls. In A. J. Wein, L. R. Kavoussi, A. W. Partin, & C. A Peters (Eds.), *Campbell-Walsh urology* (11th ed., pp. 3453–3465). Philadelphia, PA: Elsevier.

Kelly, M. M. (2010). Prematurity. In P. J. Allen, J. A. Vessey, & N. A. Schapiro (Eds.), *Primary care of the child with a chronic condition* (5th ed., pp. 756–771). St. Louis, MO: Mosby.

Levy, J., & D'Harlingue, A. E. (2013). Recognition, stabilization, and transport of the high-risk newborn. In M. H. Klaus & A. A. Fanaroff (Eds.), *Care of the high risk neonate* (6th ed., pp. 71–105). Philadelphia, PA: Saunders.

Lewis, M. (2014a). A comprehensive newborn examination: Part I. General, head and neck, cardiopulmonary. *American Family Physician,*

90, 289–296. Retrieved from https://www.aafp.org/afp/2014/0901/p289.html

Lewis, M. (2014b). A comprehensive newborn examination: Part II. Skin, trunk, extremities, neurologic. *American Family Physician, 90*, 297–302. Retrieved from https://www.aafp.org/afp/2014/0901/p297.html

Lewis, S. M., Bucher, L., Heitkemper, M. M., Harding, M. M., Kwong, J., & Roberts, D. (2017). *Medical-surgical nursing: Assessment and management of clinical problems* (10th ed.). St. Louis, MO: Elsevier.

Lissauer, T. (2015). Physical examination of the newborn. In R. J. Martin, A. A. Fanaroff, & M. C. Walsh (Eds.), *Fanaroff & Martin's neonatal-perinatal medicine: Diseases of the fetus and infant* (10th ed., pp. 391–406). St. Louis, MO: Mosby.

Liu, R. W., & Thompson, G. H. (2015). Musculoskeletal disorders in neonates. In R. J. Martin, A. A. Fanaroff, & M. C. Walsh (Eds.), *Fanaroff & Martin's neonatal-perinatal medicine: Diseases of the fetus and infant* (10th ed., pp. 1776–1785). St. Louis, MO: Elsevier.

Lubchenco, L. O. (1967). *The high risk infant*. Philadelphia, PA: Saunders.

Lubchenco, L. O., Hansman, C., & Boyd, E. (1966). Intrauterine growth in length and head circumference as estimated from live births at gestational ages from 26 to 42 weeks. *Pediatrics, 37*, 403–408. Retrieved from https://pediatrics.aappublications.org/content/37/3/403

Mangurten, H. M., Puppala, B. L., & Prazad, P. A. (2015). Birth injuries. In R. J. Martin, A. A. Fanaroff, & M. C. Walsh (Eds.), *Fanaroff & Martin's neonatal-perinatal medicine: Diseases of the fetus and infant* (10th ed., pp. 407–435). St. Louis, MO: Elsevier.

McLean, F., & Usher, R. (1970). Measurements of liveborn fetal malnutrition infants compared with similar gestation and with similar birth weight normal controls. *Biology of the Neonate, 16*, 215–221. doi:10.1159/000240279

Orge, F. H., & Grigorian, F. (2015). Examination and common problems of the neonatal eye. In R. J. Martin, A. A. Fanaroff, & M. C. Walsh (Eds.), *Fanaroff & Martin's neonatal-perinatal medicine: Diseases of the fetus and infant* (10th ed., pp. 1734–1766). St. Louis, MO: Elsevier.

Palmer, L. S., & Palmer, J. S. (2016). Management of abnormalities of the external genitalia in boys. In A. J. Wein, L. R. Kavoussi, A. W. Partin, & C. A. Peters (Eds.), *Campbell-Walsh urology* (11th ed., pp. 3368–3398). Philadelphia, PA: Elsevier.

Parikh, A. S., & Mitchell, A. L. (2015). Congenital anomalies. In R. J. Martin, A. A. Fanaroff, & M. C. Walsh (Eds.), *Fanaroff & Martin's neonatal-perinatal medicine: Diseases of the fetus and infant* (10th ed., pp. 437–457). St. Louis, MO: Elsevier.

Parry, R. L. (2015). Selected gastrointestinal anomalies in the neonate. In R. J. Martin, A. A. Fanaroff, & M. C. Walsh (Eds.), *Fanaroff & Matin's neonatal-perinatal medicine: Diseases of the fetus and infant* (10th ed., pp. 1395–1411). St. Louis, MO: Elsevier.

Robinson, S., & Cohen, A. R. (2015a). Disorders in head shape and size. In R. J. Martin, A. A. Fanaroff, & M. C. Walsh (Eds.), *Fanaroff & Martin's neonatal-perinatal medicine: Diseases of the fetus and infant* (10th ed., pp. 964–989). St. Louis, MO: Elsevier.

Robinson, S., & Cohen, A. R. (2015b). Myelomeningocele and related neural tube defenct. In R. J. Martin, A. A. Fanaroff, & M. C. Walsh (Eds.), *Fanaroff & Martin's neonatal-perinatal medicine: Diseases of the fetus and infant* (10th ed., pp. 990–992). St. Louis, MO: Elsevier.

Santos, L. S., & Smith, L. A. (2014). Well-child care for the preterm infant. In C. D. Berkowitz (Ed.), *A primary care approach* [e Version] (5th ed., Chapter 40) Retrieved from http://ebooks.aappublications.org/content/9781581108514/9781581108514

Sharma, R. K. (2014). Hypertelorism. *Indian Journal of Plastic Surgery, 47*(3), 284–292. doi:10.4103/0970-0358.146572

Sherman, J. (2015). Care of the extremely low birth weight infant. In M. T. Verklan & M. Walden (Eds.), *Core curriculum for neonatal intensive care nursing* (5th ed., pp. 427–438). St. Louis, MO: Saunders.

Sifuentes, M. (2000). Well child care for preterm infants. In C. D. Berkowitz (Ed.), *Pediatrics: A primary care approach* (2nd ed.). Philadelphia, PA: Saunders.

Singhal, V., Agal, P., & Kamath, N. (2012). Detection of fetal malnutrition by CAN score at birth and its comparison to other methods of determining intrauterine growth. *Indian Journal of Clinical Practice, 22*, 576–582. Retrieved from http://medind.nic.in/iaa/t12/i4/iaat12i4p576.pdf

Son-Hing, J. P., & Thompson, G. H. (2015). Congenital abnormalities of the upper and lower extremities and spine. In R. J. Martin, A. A. Fanaroff, & M. C. Walsh (Eds.), *Fanaroff & Martin's neonatal-perinatal medicine: Diseases of the fetus and infant* (10th ed., pp. 1789–1808). St. Louis, MO: Elsevier.

Spilman, L. (2002). Examination of the external ear. *Advances in Neonatal Care, 2*(2), 72–80. doi:10.1053/adnc.2002.32041

Stanley, F. J. (1994). Cerebral palsy trends: Implications for perinatal care. *Acta Obstetricia et Gynecologica Scandinavica (Copenhagen), 73*, 5–9. doi:10.3109/00016349409013384

Stewart, J. E., & Joselow, M. R. (2012). Follow up care of very preterm and very low birth weight infants. In J. P. Cloherty (Ed.), *Manual of neonatal care* (7th ed., pp. 185–191). Philadelphia, PA: Lippincott Williams & Wilkins.

Tappero, E. P. (2019). Musculoskeletal system assessment. In E. P. Tappero & M. E. Honeyfield (Eds.), *Physical assessment of the newborn* (6th ed., pp. 133–158). New York, NY: Springer Publishing Company.

Trotter, C. W. (2019). Gestational age assessment. In E. P. Tappero & M. E. Honeyfield (Eds.), *Physical assessment of the newborn* (6th ed., pp. 21–40). New York, NY: Springer Publishing Company.

Vargo, L. (2019). Cardiovascular assessment. In E. P. Tappero & M. E. Honeyfield (Eds.), *Physical assessment of the newborn* (6th ed., pp. 87–104). New York, NY: Springer Publishing Company.

Vogt, B. A., & Dell, K. M. (2015). The kidney and urinary tract. In R. J. Martin, A. A. Fanaroff, & M. C. Walsh (Eds.), *Fanaroff & Martin's neonatal-perinatal medicine: Diseases of the fetus and infant* (10th ed., pp. 1676–1699). St. Louis, MO: Elsevier.

Waardenburg, P. J. (1951). A new syndrome combining developmental anomalies of the eyelids, eyebrows, and nose root with pigmentary defects of the iris and head hair and with congenital deafness. *American Journal of Human Genetics, 3*, 195.

Walker, V. P. (2018). Newborn evaluation. In C. A. Gleason & S. U. Juul (Eds.), *Avery's diseases of the newborn* (10th ed., pp. 289–311). Philadelphia, PA: Saunders.

Weiner, G. M., Zaichkin, J., & Kattwinkel, J. (Eds.). (2016). *Textbook of eonatal resuscitation* (7th ed.). Elk Grove, IL: American Academy of Pediatrics & American Heart Association.

Witt, C. (2019). Skin assessment. In E. P. Tappero & M. E. Honeyfield (Eds.), *Physical assessment of the newborn* (6th ed., pp. 41–56). New York, NY: Springer Publishing Company.

Zderic, S. A. (2005). Developmental abnormalities of the genitourinary system. In H. W. Taeusch, R. A. Ballard, & C. A. Gleason (Eds.), *Avery's diseases of the newborn* (8th ed., pp. 1287–1297). Philadelphia, PA: Saunders.

Zubrow, A. B., Hulman, S., Kushner, H., & Falkner, B. (1995). Determinants of blood pressure in infants admitted to neonatal intensive care units: A prospective multicenter study. Philadelphia Neonatal Blood Pressure Study Group. *Journal of Perinatology, 15*, 470.

CHAPTER 5

Normal Term Newborn

Cheryl Riley, Becky Spencer, and Lyn S. Prater

INTRODUCTION

The nurse caring for the newborn plays a unique role in not only providing care to the newborn but also in assisting in the integration of the baby into the family. Understanding of the newborn is optimized when information related to the mother and family is known. The information from the maternal history, which includes previous health issues, as well as prenatal, intrapartum, and postpartum histories, is critical for assessing adaptation to extrauterine life. This information gives insight into the environment from which the newborn has come and therefore helps determine the nurse's plan of care. Skills of assessment, analysis, planning, implementation, and evaluation of both mother and newborn are critical and must occur in synchrony for the nurse to assist the newborn's transition from birth to discharge. See Chapter 4, Assessment of the Newborn and Infant, for a list of the components of a comprehensive maternal and neonatal history.

ADMISSION

Providing the optimal environment for the newborn begins at birth. "Mothers and babies have a physiologic need to be together at the moment of birth and during the hours and days that follow." (Crenshaw, 2014, p. 211). The healthy, stable newborn should be placed directly on the mother's bare chest immediately after birth. Initial nursing interventions after birth, such as drying the infant, initial assessment, and Apgar scoring, should occur while the baby is skin to skin. Babies having difficulty with the transition from intrauterine to extrauterine life may be placed in the radiant warmer that provides warmth and an unobstructed view of the newborn infant for further evaluation. The admission nurse receives a comprehensive report from the labor and delivery nurse, which includes the maternal history and the delivery summary. Nursing interventions including birth weight, vitamin K, and ophthalmic antibiotic administration should be delayed to allow at least 1 hour of uninterrupted skin-to-skin contact (SSC) and breastfeeding attempts. Nurses should remain with the mother during this time and assist with breastfeeding positioning and latch. Crenshaw (2014) demonstrated through a quality improvement project that skin to skin in the operating room after a cesarean can safely occur and promote exclusive breastfeeding. Risk factors alerting the nurse for possible problems are identified, and a cursory visual assessment is done to assess for any signs of maladaptation to extrauterine life.

Vital Signs

A complete physical assessment of the newborn is done on admission (see Chapter 4, Assessment of the Newborn and Infant). Vital signs are taken during the initial physical assessment and are repeated periodically according to the institution's protocol. The vital signs include temperature, respiratory rate, heart rate, rhythm, and a four-point blood pressure (see Table 5.1). **Quality and Safety: Infants at risk for hypoglycemia would require a blood glucose level to be drawn no later than 2 hours after birth** (Wight & Marinelli, 2014).

The initial temperature gives the nurse a baseline from which to evaluate the thermoregulation ability of the newborn and is taken via the axillary route. The acceptable range of values is from 35.5°C to 37.5°C. The apical heart rate is counted for one full minute, and the acceptable range is from 100 to 160 beats/minute (bpm). The respiratory rate is also counted for one full minute, and the acceptable range of values is from 30 to 60 breaths/minute, although it is not uncommon to have respiratory rates as high as 80 to 100 breaths/minute within the first 20 minutes of life, which most likely represents normal transition to extrauterine life. A four-point blood pressure is taken, and the acceptable range values are systolic 60 to 80 mmHg and diastolic from 40 to 50 mmHg. Pain is assessed as the fifth vital sign by using a pain scale (Raeside, 2011). Blood glucose should be obtained within the first 2 hours of life and after the first feeding in all newborns that are identified as high risk for the development of hypoglycemia or any newborn with signs and symptoms of hypoglycemia.

Medications

Quality and Safety: The administration of vitamin K is given as a prophylaxis for hemorrhagic disease of the newborn by the intramuscular route using the vastus lateralis muscle.

Quality and Safety: As a prophylaxis against neonatal ophthalmia due to organisms such as gonorrhea and chlamydia, erythromycin ointment is applied by placing a ribbon of medication into each eye from the inner to the outer canthus. This practice is mandated by state law and is required in all states (Mabry-Hernandez & Oliverio-Hoffman, 2010).

TABLE 5.1

NORMAL RANGE FOR VITAL SIGNS

Temperature	Respiratory Rate	Heart Rate	Blood Pressure Systolic	Blood Pressure Diastolic
35.5°C–37.5°C	30–60 breaths/minute	100–160 beats/minute	60–80 mmHg	40–50 mmHg

After signed consent at the parents' request, hepatitis B (Hep B) vaccine will be given intramuscularly. Hep B is a serious viral disease that affects the liver. This virus is spread through contact with blood or other body fluids of an infected person. The vaccine can prevent Hep B and the serious complications associated with it that include liver cancer and cirrhosis. Routine hepatitis vaccination in the United States began in 1991. Since then, the reported incidence of Hep B in children has dropped more than 95%, and by 75% in all age groups. New recommendations call for three doses of Hep B. The first dose should be given shortly after birth, the second dose 1 through 2 months, and the third dose between 6 and 18 months of life. If the mother is Hep B positive, both Hep B vaccine and Hep B immune globulin should be given within 12 hours of birth (Centers for Disease Control and Prevention [CDC], n. d.).

Measurements

Measurements of the newborn provide information for comparisons to normal growth curves and help the nurse identify potential risk factors. The newborn's length is measured from the crown of the head to the heel with the leg fully extended; it is a more accurate measurement when the baby is placed on a calibrated length board than when using measuring tape. The average newborn length is 50 cm. Head circumference is measured placing the tape measure around the fullest part of the occiput. The average head circumference is 35.5 cm. Chest circumference is measured using the nipple line as a reference point and crossing the lower border of the scapulae. The average chest circumference is 33 cm and is usually 2 to 3 cm smaller than the head. The abdominal circumference is measured at just above the umbilicus. All measurements are documented in the medical record. These measurements are plotted on a growth chart to determine if the newborn is small for gestation age (SGA), appropriate for gestation age (AGA), or large for gestation age (LGA; Kaneshiro, 2011). Growth parameters for both male and female infants help providers assess subsequent growth, development, and risk of disease.

The First Bath

The first bath is given after the newborn has achieved thermal and cardiorespiratory stability, and no sooner than 6 hours after birth to promote maternal–newborn bonding and for skin protection. This delay in bathing is a change from the previous Association of Women's Health, Obstetrics, and Neonatal Nurses (AWHONN) guidelines and serves to promote transition to extrauterine life. Potential benefits to the baby with this change include a decreased risk for hypothermia and hypoglycemia. Additionally, the vernix that remains on the skin provides a mechanical barrier with antimicrobial properties that protect the infant from infection and will be absorbed into the skin over a 24-hour period. The amniotic fluid has similar components to colostrum and should not be wiped off the baby's hands to encourage rooting for the mother's breast and suckling in preparation for breastfeeding. Prior to bathing, ensure that the bath equipment is disinfected before and after each use. The bath water should be approximately 38°C (100°F) and the room temperature should be between 26°C and 27°C (79°F–81°F; Fort & Walker, 2015). It is important to keep the duration of the bath to a minimum. A mild pH-neutral cleanser may be used to remove blood and amniotic fluid (AWHONN, 2014). Dry the newborn with prewarmed towels or blankets and place in SSC with the mother or on a preheated radiant warmer if skin-to-skin placement is not possible.

Cord Care

During the first bath, clean the umbilical cord and surrounding skin to remove debris. Dry the cord with clean absorbent gauze and leave uncovered. Allow the cord to dry naturally. These means keep the umbilical cord area clean and dry without the routine use of topical agents. Keep the diaper folded down to leave the cord uncovered to help prevent contamination with urine and/or stool. The routine use of antimicrobial agents such as isopropyl alcohol, povidone-iodine, topical antibacterial agents, and triple dye is not recommended (AWHONN, 2014). If there is redness, swelling, or drainage, it may be a sign of infection and should be reported to the primary care provider.

SECURITY

Safety and security measures are important components of any environment that provides care to newborns. Institutions are required to have a safety and security system in place to ensure the infant's safety during its birth hospitalization. These systems also provide parents with the reassurance that their baby is safe not only from internal threats, but from external ones as well.

Identification bracelets are placed at birth with a printed number on each of the bracelets, along with the identifying information of the mother, including birth date, birth time, and gender. Typically, two bracelets are placed on the baby: one on the wrist and one on the leg. Another bracelet is placed on the mother, and the fourth bracelet is placed on the father or significant other. Wearing the matching bracelet means that the person is allowed the privilege of receiving the baby from the nursery nurse or taking the baby from the nursery. These bracelets are also used to match the baby with mother every time the baby is brought to the room or taken from the nursery. **Quality and Safety: This is an important policy that assures that the baby is always given to the correct mother, including upon discharge.**

Security sensors can be placed either on the umbilical cord via the cord clamp or on the leg with a strap. These sensors monitor the baby's location at all times and will send out a signal if the sensor passes too close to an open elevator or stairwell door. These tracking systems vary from institution to institution but are usually connected to the security systems of the hospital. **Emergency Alert: Whenever the alarm is set off or activated, a "Code Pink" is broadcasted throughout the hospital and security personnel**

are deployed to that area of the hospital for follow-up. The security sensors are then removed prior to discharge.

An *ID Badge* with the healthcare employee's picture and name are now required by most institutions while the employee is on duty. Many institutions also use a color-coded badge to identify which healthcare workers are allowed to transport the baby from the mother's room to the newborn nursery and back. This safety measure is in place to assure that only qualified employees care for the newborn infants.

Passwords are used at many institutions as another form of security to identify employees who are allowed to transport newborns. These passwords are typically changed daily, and the parents will be given the new password at the beginning of the nursing shift. Parents are requested to ask anyone who attempts to take their baby out of their room for the password of the day. If the transporter cannot tell them the correct password for the day, the parents should call the newborn nursery for help before allowing the newborn to be taken.

Teaching the parents how to use the *bulb syringe* to clear oral or nasal secretions is an important aspect of the newborn nurse's initial visit, along with showing the parents how to use the *emergency call button*. Demonstrating how to use these two safety measures along with requesting the mother to repeat the demonstrations helps assure the newborn nurse that the baby is in a safe environment.

BACK TO SLEEP

In 1994, the National Institute of Child Health and Human Development along with American Academy of Pediatrics (AAP) launched the Back to Sleep campaign in an effort to reduce the risk of sudden infant death syndrome (SIDS). There are approximately 3,500 infant sleep-related deaths annually, including SIDS, accidental strangulation, and suffocation, along with ill-defined deaths. After the initial decline of sleep-related deaths with the Back to Sleep campaign, there has been little reduction in recent years. In its 2016 update, the AAP recommends a safe sleep environment to reduce the risk of all sleep-related deaths (AAP, 2016). A safe sleep environment includes supine positioning, the use of a firm sleep surface, room sharing without bed sharing, and the avoidance of soft bedding and overheating. They further recommended the avoidance of exposure to smoke, alcohol, and illicit drugs and promoting breastfeeding, routine immunizations, and use of a pacifier (AAP, 2016).

In the newborn nursery, infants are placed on their backs in the cribs, and this practice is taught to parents as a part of the initial safety teaching protocol. Studies show that parents take their cues from the nurses in the nursery regarding the handling and positioning of their infant. This role-modeling behavior of nurses is a critical way for information to be transferred to parents (Carrier, 2009). Teaching the parents about a safe sleep environment is important due to the direct correlation between increased infant mortality and where and how infants sleep (AAP, 2016; Ibarra & Goodstein, 2011).

DAILY CARE

The daily care of the newborn includes obtaining the weight every 24 hours and documenting it in the medical record. If the newborn has lost more than 7% of his or her birth weight, the primary care provider should be notified.

Vital signs are obtained and documented at every shift. Any abnormal value should be reported, and more frequent assessments of vital signs may be required.

Reviewing the intake and output is an important parameter to measure the nutritional status of the newborn. Many times, this form is filled out by the parents and may require verification for any missing information.

The newborn should void within the first 24 hours of life and stool within the first 48 hours of life. If this does not occur, the primary care provider should be notified.

Lactation consultants should be available for all breastfeeding mothers.

A physical examination is completed every shift and documented in the medical record. Any abnormalities should be reported to the primary care provider.

Discharge teaching begins at admission and continues throughout the birth hospitalization.

CIRCUMCISION

The issue of circumcision has long been debated as to its medical necessity, and the newest task force statement on circumcision by the AAP in 2017 calls both providers and consumers to be educated on the risks and benefits of routine circumcisions to be able to make informed decisions. While neonatal circumcision is cited as one of the most commonly performed procedures in the United States today (Ahmed & Ellsworth, 2012), it is a topic that healthcare providers must be able to discuss with their patients. Whether parents decide to have their male infants circumcised, the decision should be made only after appropriate counseling by their primary healthcare provider so that they may make an informed decision.

The nurse caring for the newborn who is to be circumcised must ensure that the proper consent form has been signed by the parent, assemble necessary equipment for the procedure, and then participate in the "time-out" surgical protocol before the care provider initiates the surgical procedure. Because circumcision is a painful procedure, pain management techniques must be implemented before, during, and after the procedure. Before the procedure, it is common for the care provider to order a topical analgesic cream that should be applied 20 to 30 minutes before the surgical procedure. During the procedure, the newborn is swaddled in blankets with only the groin area exposed while being strapped to the circumcision board. This swaddling provides for tactile comfort and warmth while being securely strapped to the board. Giving the newborn an oral sucrose solution along with nonnutritive sucking has been shown to decrease the infant's pain during the circumcision (Hardcastle, 2010). Utilizing a dorsal penile block or ring block by the care provider in combination with the administration of sucrose and analgesic cream provides the best pain relief for the newborn during circumcision (AAP Policy Statement, 2012). **Emergency Alert: After the circumcision, it is important to monitor the newborn's pain response and treat with acetaminophen as necessary for the first 24 hours post procedure. It is also imperative that the nurse monitor for bleeding at the site as well as prevent infection.** Depending upon the type of circumcision device used, a petroleum jelly dressing should be applied to keep the wound from adhering to the diaper. This dressing should be changed after every void or stool to maintain cleanliness at the surgical site. Teaching the parents to care for the circumcised penis is important during hospitalization as well as in preparation for discharge. This should include cleansing the area with water at each diaper change, monitoring for signs and symptoms of infection, and refraining from tugging at the Plastibell ring until it falls off on its own.

There are basically three types of circumcision devices used in the United States today: the Gomco or Yellen clamp, the Plastibell,

and the Mogen clamp. The type chosen by the care provider is usually determined by which device was in use during their medical training program. The most important factor is that the healthcare professional performing the procedure is familiar with the equipment or device he or she is using (Angel, 2018). Whichever device is used, it is the nurse's responsibility to ensure that the equipment is sterile and in good working order and that appropriate sizes are available for use.

NEONATAL THERMOREGULATION

Thermoregulation is the ability to balance heat production and heat loss in order to maintain normal body temperature. The infant loses heat by evaporation, convection, conduction, and radiation. Evaporation is heat loss that occurs by the evaporation of water from the skin and respiratory tract. Convection is heat loss from cooler surroundings such as the delivery room. Conduction is heat loss to cooler objects that are in direct contact with the infant such as a cold bed. In contrast with conduction, radiation is heat loss to cooler objects where there is no direct contact. Evaporation of amniotic fluid from the infant's skin in the delivery room is the main source of heat loss in the initial newborn period. Normal adaptation to extrauterine life requires minimizing all the mechanisms for heat loss. The goal of care is to maintain a neutral thermal environment for the infant in whom heat balance is maintained (Ringer, 2013).

Nonshivering Thermogenesis

A thermogenic response begins within the first few minutes of life. There are two mechanisms for heat production. First, there is an increase in cellular metabolic activity primarily in the brain, heart, and liver; second, heat is produced by nonshivering thermogenesis (NST). NST is the primary source of heat production and entirely depends on brown adipose tissue. Brown adipose tissue is deposited after 28 weeks' gestation and is primarily found around the scapulae, kidneys, adrenals, neck, and axilla. Heat is produced by uncoupling adenosine triphosphate synthesis via the oxidation of fatty acids in the mitochondria, utilizing uncoupled protein (Ringer, 2013). Brown fat has an increased vascular and nerve supply that other fats do not. Significant lipid metabolic activity in the brown fat can warm the infant by increasing heat production by 100%. Brown fat stores are usually present for several weeks after birth, but are rapidly depleted in the presence of cold stress (Stavis & Mawr, 2017).

Cold Stress

The presence of cold stress increases metabolic and physiologic demands on all infants. When an infant has cold stress, there is an increase in oxygen consumption and energy is shifted from maintaining normal function of vital organs to thermogenesis for survival. If adequate oxygen tension cannot be maintained, there is vasoconstriction that can lead to increased pulmonary pressure. This causes a decrease in the partial pressure of arterial oxygen and blood pH. These changes may prevent the ductus arteriosus from closing and cause a right to left shunt. The basal metabolic rate also increases with cold stress; if cold stress is prolonged, it can lead to lactic acid production, which causes metabolic acidosis (Stavis & Mawr, 2017).

Management

In cases of mild hypothermia (36.0°C–36.4°C), the infant can be rewarmed by SSC in a warm room. This entails placing the infant with only a diaper directly on the mother's bare chest and covering them both with a blanket with the infant's head exposed. With moderate hypothermia (32.0°C–35.9°C), the infant should be placed on a radiant warmer or a preheated isolette set at 35.0°C to 36.0°C. In cases of severe hypothermia (<32°C), the infant should be rewarmed on a radiant warmer over several hours. Feeding should be continued to provide calories and fluid to prevent hypoglycemia, which is common in infants experiencing hypothermia.

Hyperthermia

Hyperthermia is less common than hypothermia but does occur and needs to be corrected. Hyperthermia is defined as a body temperature greater than 37.5°C. The most common cause for hyperthermia is excess environmental heat. It is important to differentiate hyperthermia from fever, which is a raised body temperature in response to infection and/or inflammation. Although it is not possible to distinguish between fever and hyperthermia based on the measurement of body temperature alone, infection should always be considered first. Assessment of the environmental factors such as the mode and temperature that the radiant warmer is set on and the number of blankets the infant is swaddled in is necessary. Steps should be taken to correct any environmental factors present. The clinical appearance of the infants often indicates the causative mechanism. Any signs and symptoms of infection should be reported to the healthcare provider.

GLUCOSE HOMEOSTASIS

Glucose provides the metabolic fuel for the developing fetus. While in utero, the fetus receives a constant supply of glucose from the mother by facilitated diffusion across the placenta. After birth, when the cord is cut, the supply of glucose stops, which requires the infant to begin to regulate the concentrations of insulin. Lower glucose levels are typically seen in healthy infants in the first 48 hours of life (Thompson-Branch & Havranek, 2018). This mechanism is present in all mammals, which may indicate normal adaptation to extrauterine life.

The infant requires a higher glucose infusion rate when compared to older children and adults primarily due to the larger brain-to-body mass ratio in infants. Therefore, it is important for the infant to maintain regular and frequent feeds every 2 to 3 hours during the first few days of life. If the infant is unable to meet the metabolic demand, it may lead to hypoglycemia. Severe and prolonged hypoglycemia may result in seizures and abnormal neurologic outcomes, though it is not known at what specific value of glucose these outcomes occur and the duration of the hypoglycemic event (Thompson-Branch & Havranek, 2018).

Management of low glucose levels in the first 48 hours of life is one of the most frequent issues encountered in the newborn. The screening and management of hypoglycemia is based on identified risk factors that include symptoms of hypoglycemia, LGA, perinatal stress including birth asphyxia, preeclampsia, intrauterine growth restriction (IUGR), meconium aspiration, erythroblastoma, polycythemia, hypothermia, preterm and post term, infant of a diabetic mother (IDM), family history and genetic disorders, and late-preterm infants born between 34 and 36 completed weeks of gestation. An expert panel convened by the National Institutes of Health (NIH) in 2008 concluded that there is not an evidence-based definition for clinically significant neonatal hypoglycemia, especially regarding how it relates to brain injury, which remains true even today. Blood glucose concentrations as low as 30 mg/dL are common in healthy infants by 1 to 2 hours after birth and are usually transient, asymptomatic,

and considered part of the normal adaptation to extrauterine life. Most infants will compensate for this physiologic hypoglycemia by producing alternate energy sources such as ketone bodies, which are released from fat. Clinically significant hypoglycemia, on the other hand, reflects an imbalance between the supply and use of glucose and alternative fuels (Adamkin, 2018).

Hypoglycemia is most common in infants that are SGA, IDM, and late-preterm infants. It remains unclear if otherwise healthy infants that are LGA are at risk for hypoglycemia because it is difficult to exclude maternal diabetes or maternal hyperglycemia with standard glucose tolerance tests. Therefore, screening should be reserved for the at-risk infants. Routine glucose screening is not necessary in healthy term newborns after a normal pregnancy and delivery. In any infant with signs and symptoms of hypoglycemia, blood glucose should be collected and sent to the laboratory as soon as possible. Breastfed infants have a lower concentration of serum glucose but a higher concentration of ketone bodies when compared to formula-fed infants. It is hypothesized that breastfed infants tolerate lower serum glucose concentrations without signs and symptoms because of the increased ketone levels (Adamkin, 2011).

Screening

IDMs may develop asymptomatic hypoglycemia as early as 1 hour after birth and up to 12 hours of age. While SGA or LGA infants may develop hypoglycemia as early as 3 hours of age, they may be at risk for up to 10 days. Because of this, decisions related to how often to obtain glucose levels are based on the infants' individual risk factors. Screening for the asymptomatic at-risk infants should be performed within the first few hours of life and continue through several feedings. SGA infants should be fed every 2 to 3 hours and have their glucose checked prior to each feed for the first 24 hours. After that, if the glucose checks before every feed may be discontinued. Due to the limitations of point of care monitoring, a blood or serum glucose must be confirmed by the laboratory. If there is a delay in processing the sample, it can give a falsely low value due to the metabolism of glucose by the erythrocytes. Treatment of low point of care results should not be delayed while waiting for laboratory results (Adamkin, 2018).

Currently, there is discussion between the AAP and the Pediatric Endocrine Society (PES) regarding the management of hypoglycemia and at what glucose level to treat. The AAP admits that the definition of hypoglycemia, a blood glucose of less than 47 mg/dL, is based on observational studies. The PES recommends treatment of glucose levels less than 50 mg/dL within the first 48 hours. The PES also suggests that if there is concern regarding a congenital hypoglycemia disorder, the threshold should be 60 mg/dL (Adamkin, 2018).

Management

Signs and symptoms of hypoglycemia include jitteriness, cyanosis, seizures, apneic episodes, tachypnea, weak or high-pitched cry, decreased tone, lethargy, poor feeding, and eye rolling. It is important to assess for underlying conditions such as sepsis. **Emergency Alert: Coma and seizures may occur with prolonged and repetitive hypoglycemia, usually less than 10 mg/dL.** Because of the risk of brain injury, special attention should be paid to neurologic signs and symptoms (Adamkin, 2018).

The recommendations shown in Figure 5.1 for the treatment of hypoglycemia are divided into two time periods that reflect the changing glucose levels within the first 12 hours of life. This algorithm provides a range of options for the treatment of hypoglycemia that include refeeding or giving intravenous (IV) glucose. The target glucose range is greater than or equal to 45 mg/dL prior to each feed. Infants that are at risk should be fed within the first hour of life and screened 30 minutes after the feeding. This recommendation is consistent with that of the World Health Organization (WHO). If the infant does not feed well, gavage feedings can be considered. LGA and IDMs should be screened prior to each feeding for 12 hours, with a goal of a glucose level greater than 40 mg/dL prior to each feed. SGA and late-preterm infants should be screened for the first 24 hours. Glucose levels should be stable for a minimum of three feedings prior to discharge (Adamkin, 2018).

New Therapies

In a benchmark study, the use of buccal glucose demonstrated lower neonatal intensive care unit (NICU) admission rates related to hypoglycemia and improved breastfeeding rates while keeping the mothers and their babies together (Rozance & Hay, 2016). Makker et al. (2018) reported using 40% glucose gel (200 mg/kg or 0.5 mL/kg) as a supplement to feeding at-risk infants in the newborn nursery, which reduced the need to transfer to the NICU and the administration of IV dextrose. Results of this study demonstrated a reduction in the need to transfer to a higher level of care from 8.1% in the first year to 3.7% in the second year. Exclusive breastfeeding rates increased from 6% to 19% in the two years.

HYPERBILIRUBINEMIA

Jaundice is the most common clinical diagnosis affecting approximately 80% of all newborns in the United States (Bhutani, Vilms, & Hamerman-Johnson, 2010; Ullah, Rahman, & Hedayati, 2016). Jaundice is caused by an elevation in unconjugated (indirect) and/or conjugated (direct) bilirubin levels. Bilirubin is an antioxidant in low levels and a potent neurotoxin in high levels. Elevations in bilirubin are either due to an increase in production (breakdown of heme-containing proteins) and/or a delay in the elimination of bilirubin as well as the reabsorption of bilirubin through the enterohepatic pathway (Bhutani et al., 2010).

Seventy-five percent of bilirubin comes from the breakdown of red blood cells and 25% from ineffective erythropoiesis in the bone marrow and breakdown of tissue heme and heme proteins by the liver (Dennery, Seidman, & Stevenson, 2001). Heme is degraded by heme oxygenase, resulting in the release of iron and the formation of carbon monoxide and biliverdin. Biliverdin is then reduced to bilirubin by biliverdin reductase. The bilirubin that is formed is taken up by the liver, bound to protein Y or ligandin, and conjugated in the smooth endoplasmic reticulum with glucuronides to form bilirubin monoglucuronide in a reaction catalyzed by uridine diphosphate and monophosphate glucuronosyltransferase. The now water-soluble bilirubin glucuronide is excreted into the intestinal lumen to be eliminated in stool. The conjugated bilirubin can be deconjugated by the intestinal enzyme beta-glucuronidase and reabsorbed into circulation intestinally. This process is known as the enterohepatic pathway (Bhutani et al., 2010; Ullah et al., 2016).

Physiologic Jaundice

Physiologic jaundice in the healthy term newborn follows a typical pattern and does not present within the first 24 hours of life. The average total serum bilirubin (TSB) usually peaks at 5 to 6 mg/dL on the third to fourth day of life, then declines over the first week of life. Bilirubin levels increase to 12 mg/dL in approximately 6.1% of healthy newborns and increase to 15 mg/dL in only 3% of healthy newborns (Bhutani et al., 2010; Blackwell, 2003; Ullah

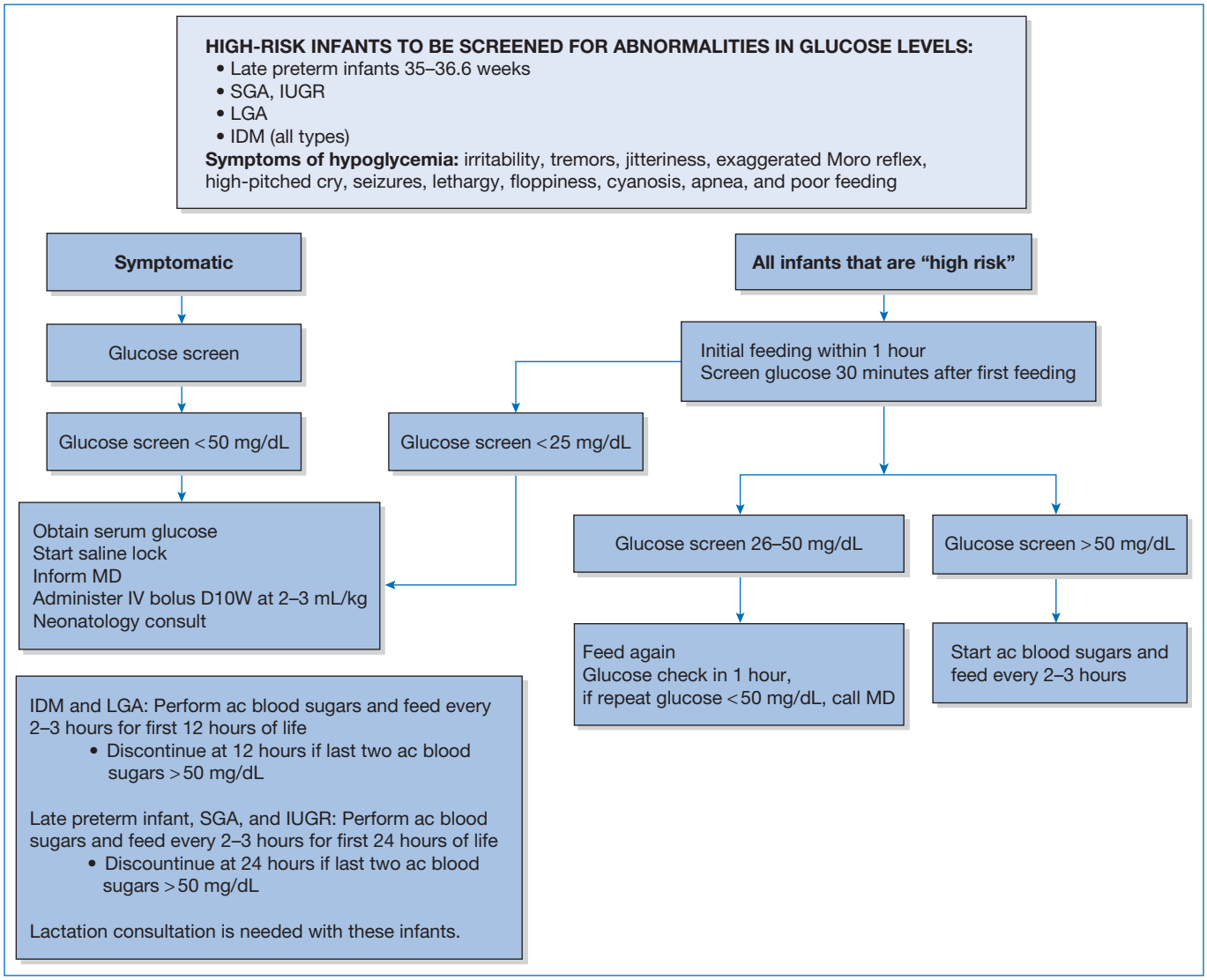


FIGURE 5.1 Screening and management of hypoglycemia.

IDM, infant of a diabetic mother; IUGR, intrauterine growth restriction; LGA, large for gestation; SGA, small for gestation.

Source: From Adamkin, D. H. (2011). Clinical report-postnatal glucose homeostasis in late-preterm and term infants. *Pediatrics, 127*(3), 575–579. doi:10.1542/peds.2010-3851

et al., 2016). Factors that contribute to the development of hyperbilirubinemia include relative polycythemia, shortened erythrocyte life span, immature hepatic uptake and conjugation processes, and increased enterohepatic circulation. Additional risk factors that increase the risk of hyperbilirubinemia are having a previous sibling with jaundice, advanced maternal age, diabetics, first trimester bleeding, prematurity, male sex, cephalohematoma or significant bruising, isoimmune or other hemolytic anemia, and Asian, American Indian, and Greek ethnicity (Khurshid & Medves, 2017).

Breastfeeding Jaundice

Breastfed newborns may be at an increased risk for developing early-onset jaundice due to decreased volume and frequency of feeding, which may result in mild dehydration and delayed passage of meconium. When compared to formula-fed newborns, breastfed newborns are 12% to 13% more likely to have peak serum bilirubin levels of 12 mg/dL. These newborns require frequent feeding, and mothers should be encouraged to breastfeed often. If there is significant (8%–10%) weight loss, decreased stooling, and decreased nutritional intake, supplementation with expressed breast milk or formula may be needed (Ullah et al., 2016).

Breast Milk Jaundice

Breast milk jaundice occurs later in the newborn period, and the incidence is 2% to 4% in term newborns. The bilirubin begins to rise around day of life 4 and continues to rise and may reach 20 mg/dL by day of life 14 and remain elevated for 2 weeks. The underlying cause of breast milk jaundice is unknown. The breast milk may have substances such as beta-glucuronidase and nonesterified fatty acids that may inhibit normal bilirubin metabolism. If breastfeeding is discontinued, there will be a rapid decline in bilirubin within 48 hours, confirming the diagnosis. During this time, it is important to encourage mothers to continue to pump their breast milk to enable continued breastfeeding. There is only a small increase in the bilirubin when breastfeeding is resumed. Mothers of newborns with breast milk jaundice have a 70% chance of this reoccurring with future pregnancies (Ullah et al., 2016).

Pathologic Jaundice

Pathologic jaundice in term infants is diagnosed if jaundice appears within the first 24 hours of life, after the first week of life, or lasts greater than 2 weeks. TSB that rises by greater than 5 mg/dL/day

or TSB greater than 18 mg/dL is also considered pathologic. Term infants who show signs and symptoms of underlying illness need further evaluation. Some of the most common pathologic causes of pathologic jaundice are immune and nonimmune hemolytic anemia, G6PD deficiency, hematoma resorption, sepsis, and hypothyroidism (Alkalay, Bresee, & Simmons, 2010; Alkalay & Simmons, 2005). Approximately 5% to 11% of term infants will develop severe hyperbilirubinemia, which is defined as a TSB greater than the 95th percentile for age in hours, and require phototherapy (Bhutani et al., 2010; Ullah et al., 2016).

Acute Bilirubin Encephalopathy and Kernicterus

Acute bilirubin encephalopathy (ABE) and kernicterus is a preventable form of neonatal bilirubin-related brain injury. ABE is a clinical central nervous system finding that is caused by bilirubin toxicity to the basal ganglia and various brainstem nuclei that is seen in the first few weeks of life. In the early stage of ABE, the severely jaundiced infant will become lethargic and hypotonic and have a poor suck. The next stage is characterized by moderate stupor, irritability, and hypertonia. The infant may also develop a fever and/or a high-pitched cry that may alternate with hypotonia and drowsiness. The hypertonia may present with arching of the neck and trunk. There is evidence that an exchange transfusion at this stage can reverse the central nervous system changes. The advanced stage is characterized by probable permanent central nervous system damage, pronounced retrocollis, opisthotonos, shrill cry, inability to feed, apnea, fever, deep stupor to coma, seizures, and death (CDC, 2016a).

Kernicterus is the chronic form of ABE in surviving infants. It is characterized by some or all of the following: athetoid cerebral palsy, auditory dysfunction, dental enamel dysplasia, paralysis of upward gaze, and occasional intellectual and other handicaps. The hallmark sign of kernicterus is the icteric staining of the basal ganglia, which is usually found at autopsy. Injury occurs when the TSB levels exceed the infant's neuroprotective defenses and result in neuronal damage. Risk factors for kernicterus are late-preterm birth, plethora, hemolytic disease, and genetic abnormalities as well as complications from dehydration, sepsis, acidosis, poor feeding, and hypoalbuminemia (Bhutani et al., 2010; CDC, 2016a; Ullah et al., 2016).

Assessment

Assessment of hyperbilirubinemia should be done through diagnostic testing and screening and not by visual inspection alone. Screening tests for hyperbilirubinemia consist of assessing clinical risk factors and measuring bilirubin levels either by serum or transcutaneously (TcB), and plotting them on an age in hour-specific bilirubin nomogram (see Figure 5.2). This range of TSB levels rather than one specific level provides the threshold for the onset of neurotoxicity. Predischarge assessment by either a TSB or TcB measurement that is plotted on an age in hour-specific nomogram that identifies risk zones should be done on all infants. This provides a simple and accurate method of identifying the risk that a newborn will develop hyperbilirubinemia that requires treatment after discharge. The AAP Subcommittee on Hyperbilirubinemia (2004), Canadian Paediatric Society (2007), National Association of Neonatal Nurses Board of Directors (2011), and Okwundu et al. (2017) recommend the following clinical practices:

- Successful breastfeeding should be promoted and supported to decrease the incidence of severe hyperbilirubinemia.
- Nursery protocols for the identification and evaluation of hyperbilirubinemia should be established.
  - Hospitals should adapt facility-wide policies and procedures that maintain an adequate standard of care for all newborns in order to prevent ABE and kernicterus.
  - Bilirubin levels should be carefully monitored in infants found to be jaundiced in the first 24 hours of life.
  - Jaundice should be assessed regularly at least every 8 to 12 hours, and nurses should have independent authority to obtain a TSB or TcB level.
- Education for healthcare providers must emphasize that visual inspection is not reliable as the sole method for assessing jaundice.
- Bilirubin levels must be interpreted according to the infant's age in hours.
- Closer surveillance of infants with a gestational age of less than 38 weeks is necessary because of their higher risk for severe hyperbilirubinemia.
- All infants should be assessed for adequacy of breastfeeding and for the risk of severe hyperbilirubinemia before discharge. Universal discharge screening should be combined with an assessment of clinical risk factors (of which gestational age and exclusive breastfeeding are the most important) and a targeted follow-up.
- Parents should receive written and verbal information about jaundice.
- Follow-up care should be based on time of discharge and risk assessment.
- Phototherapy and exchange transfusion are to be used for treatment when indicated.
  - All nurseries should have the equipment to provide intensive phototherapy.
  - Breastfeeding should be encouraged for the infant receiving phototherapy or nutritional supplementation.
- Directive that bilirubin levels must be evaluated according to the infant's age in hours, not days.
- Underscoring of the increased risk of hyperbilirubinemia in infants less than 38 weeks' gestation.
- Directive that risk assessment must be included in the evaluation of all newborns (Bhutani et al., 2010; Okwundu et al., 2017).

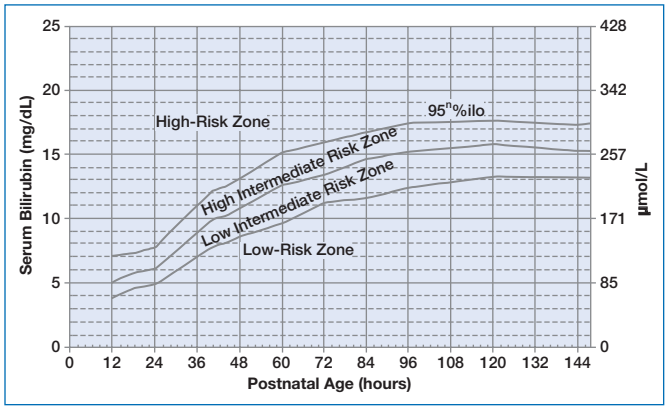


FIGURE 5.2 Nomogram for designation of risk in 2,840 well newborns at 36 or more weeks' gestational age with birth weight of 2,000 g or more or 35 or more weeks' gestational age and birth weight of 2,500 g or more based on the hour-specific serum bilirubin values.

Source: With permission from Blackwell, J. T. (2003). Clinical practice guidelines. Management of hyperbilirubinemia in the healthy term newborn. *Journal of the American Academy of Nurse Practitioners, 15*(5), 194–198. doi:10.1111/j.1745-7599.2003.tb00358.x

Management

Phototherapy is used to decrease the TSB level and prevent the accumulation of bilirubin in the brain. The photoisomerization of bilirubin begins as soon as the light is turned on. The light causes the bilirubin molecules to undergo quick photochemical reactions that form nontoxic, excretable isomers. These isomers have different shapes when compared to the conjugated bilirubin. They can be excreted into the bile without conjugation or special transport carriers. This effective process has almost eliminated the need for exchange transfusions and is one of the most effective treatments to prevent severe hyperbilirubinemia (Stokowski, 2011).

Factors that affect the dose of phototherapy include the spectral qualities of the light source, the intensity of the light, the distance between the light and the infant, and the amount of surface area exposed. The blue, green, and turquoise lights are considered the most effective. With regard to the number of devices used, phototherapy can be ordered as single, double, triple, or quadruple. Fiberoptic blankets may also be used. The pad containing fiberoptic fibers can be placed against the skin and remains cool. Due to the spectral power of the pad alone, it is commonly used in combination with overhead lights (Muchkoswski, 2014; Stokowski, 2011).

Opaque eye shields are required during phototherapy to protect the eyes from retinal damage. During the assessment of the infant, the phototherapy lights should be turned off and the eye shields removed to assess the eyes for drainage, edema, and redness. Complications of eye shields include eye irritation, corneal abrasion, blocked tear ducts, and conjunctivitis. Eye care is important and should include cleaning the eyes with sterile water or saline. A separate cleaning pad should be used for each eye and should be cleaned from the inner canthus outward. Sterile gloves should be worn while providing eye care. Some phototherapy units produce heat, and the infant's temperature must be monitored to avoid overheating. Phototherapy can also cause diarrhea and water loss in stools. It is important to monitor for skin breakdown in the perianal area and use protective barriers if needed (Muchkowski, 2014; Stokowski, 2011).

During phototherapy, the infant is separated from the mother, which has the potential to interfere with lactation. As long as the hyperbilirubinemia is not severe, the phototherapy can be interrupted to allow for breastfeeding and skin-to-skin care. Eye shields can be removed during this time (Muchkowski, 2014; Stokowski, 2011).

FEEDING THE HEALTHY NEWBORN

Human milk provides optimal nutrition for infants. The AAP Policy Statement on Breastfeeding and the Use of Human Milk (Eidelman & Schanler, 2012) recommends exclusive breastfeeding for 6 months and continued breastfeeding through the first year of life with the introduction of solid foods. Breastfeeding beyond 1 year of age is also supported if mother and baby so desire. Many health benefits for infants and children have been attributed to breastfeeding and are confirmed through systematic literature reviews and meta-analyses. Breastfeeding is associated with the following:

- Protection against necrotizing enterocolitis (NEC) for preterm infants (Holman et al., 2006; Ip et al., 2007; Quigley, Henderson, Anthony, & McGuire, 2007)
- Protection against SIDS; exclusive breastfeeding provides the strongest protection against SIDS (Hauck et al., 2011; Ip et al., 2007; Thompson et al., 2017; Vennemann et al., 2009)
- Protection against respiratory infections and reduced risk of hospitalization and mortality when compared with formula-fed infants (Horta & Victora, 2013; Ip et al., 2007)
- Protection against gastrointestinal infections and diarrhea (Duijts, Jaddoe, Hofman, & Mall, 2010; Horta & Victora, 2013; Ip et al., 2007)
- Protection against acute otitis media (AOM): children who are breastfed longer than 4 to 6 months had a significant reduced risk for incidence of AOM (Bowatte et al., 2015; Duijts et al., 2010; Ip et al., 2007)
- Protection against dental caries: longer duration of breastfeeding increases protection against dental caries (Avila, Pordeus, Paiva, & Martins, 2015; Tham et al., 2015)
- Protection against malocclusions: the longer infants were breastfed, the less likely they were to have malocclusions later in childhood (Peres, Cascaes, Nascimento, & Victora, 2015)
- A reduced risk of developing childhood leukemia: specifically, breastfeeding for 6 months or longer was associated with a reduced risk of acute lymphocytic leukemia (Amitay & Keinan-Boker, 2015; Ip et al., 2007)
- Possible protection against developing asthma later in childhood (Ip et al., 2007; Peres et al., 2015)
- Possible protection against developing type 1 and/or type 2 diabetes (Horta, Loret de Mola, & Victora, 2015; Ip et al., 2007)
- Possible protection against obesity later in life (Horta et al., 2015; Ip et al., 2007)

Breastfeeding also has an economic impact on the health. Bartick and Reinhold (2010) conducted a breastfeeding cost analysis related to the following pediatric diseases: NEC, otitis media, gastroenteritis, hospitalization for lower respiratory tract infections, atopic dermatitis, SIDS, childhood asthma, childhood leukemia, type 1 diabetes, and childhood obesity. The authors calculated a $13 billion per year savings in healthcare costs if 90% of mothers would breastfeed their infants exclusively for 6 months. A cost analysis of suboptimal breastfeeding rates was conducted and revealed that $14.2 billion was attributed to infant premature death from SIDS and NEC and maternal premature death from heart disease, breast cancer, and diabetes (Bartick et al., 2017).

All healthcare professionals who provide care to women of childbearing age and their children have an obligation to recommend, promote, and educate women and their support persons about breastfeeding. In 1991, the WHO and United Nations Children's Fund (UNICEF) created the Baby Friendly Hospital Initiative (BFHI) to offer recognition to hospitals and birthing centers worldwide that provide the optimal environments for breastfeeding initiation. Hospitals and birthing centers can receive the Baby Friendly designation when they fully implement and demonstrate the *Ten Steps to Successful Breastfeeding* as outlined by WHO and UNICEF (2018). To date, over 19,000 hospitals and birthing centers worldwide have achieved the Baby Friendly designation. In the United States, 527 hospitals and birthing centers are currently designated Baby Friendly (Baby Friendly USA, 2018). A systematic review of 58 experimental and quasi-experimental studies that examined the impact of the BFHI 10 steps on breastfeeding intention, duration, and exclusivity was conducted in 2016 (Pérez-Escamilla, Martinez, & Segura-Pérez, 2016). The authors found that hospitals who adhered to the BFHI 10 steps had mothers who breastfed longer, and there was a dose–response between the number of 10 steps implemented in hospitals and improved breastfeeding outcomes. In 2018, WHO and UNICEF updated the *Ten Steps to Successful Breastfeeding* to include improved guidance for implementation within healthcare facilities (Table 5.2).

TABLE 5.2

WHO/UNICEF BABY FRIENDLY HOSPITAL INITIATIVE

Ten Steps to Successful Breastfeeding (Revised 2018)	
Critical management procedures	1a. Comply fully with the *International Code of Marketing of Breast-Milk Substitutes* and relevant World Health Assembly resolutions.
	1b. Have a written infant feeding policy that is routinely communicated to staff and parents.
	1c. Establish ongoing monitoring and data management systems.
	2. Ensure that staff have sufficient knowledge, competence, and skills to support breastfeeding.
Key clinical practices	3. Discuss the importance and management of breastfeeding with pregnant women and their families.
	4. Facilitate immediate and uninterrupted skin-to-skin contact and support mothers to initiate breastfeeding as soon as possible after birth.
	5. Support mothers to initiate and maintain breastfeeding and manage common difficulties.
	6. Do not provide breastfed newborns any food or fluids other than breast milk, unless medically indicated.
	7. Enable mothers and their infants to remain together and to practice rooming-in 24 hours a day.
	8. Support mothers to recognize and respond to their infants' cues for feeding.
	9. Counsel mothers on the use and risks of feeding bottles, teats, and pacifiers.
	10. Coordinate discharge so that parents and their infants have timely access to ongoing support and care.

Source: From World Health Organization. *(2018). Ten steps to successful breastfeeding* (revised 2018). Retrieved from http://www.who.int/nutrition/bfhi/ten-steps/en

NURSING INTERVENTIONS THAT PROMOTE SUCCESSFUL BREASTFEEDING

Skin to Skin

Providing the optimal breastfeeding environment begins at birth. The healthy, stable newborn should be placed directly on the mother's bare chest immediately after birth. Initial nursing interventions after birth including drying the infant, initial assessment, and Apgar scoring should occur while the baby is skin to skin with the mother. Nursing interventions including birth weight, vitamin K, and ophthalmic antibiotic administration should be delayed to allow at least 1 hour of uninterrupted SSC and breastfeeding attempts. Nurses should remain with the mother during this time and assist with breastfeeding positioning and latch. SSC should also be maintained when possible during painful procedures including heelsticks, venous puncture, and injections because SSC during painful procedures reduces the neonates' pain response (Johnston et al., 2014).

The 2016 Cochrane Review (Moore, Bergman, Anderson, & Medley) regarding early SSC of mothers and healthy infants revealed empirical evidence that early and frequent SSC promotes stability of the cardiorespiratory system in the neonate and higher blood glucose levels. Neonates who received SSC had similar body temperature when compared to infants who did not receive SSC. Women who experienced SSC after vaginal birth reported longer durations of and exclusive breastfeeding compared to women who did not experience SSC. SSC in the operating room after a cesarean can safely occur and promote exclusive breastfeeding (Berg & Hung, 2011; Stone, Spencer, & Prater, 2014). Earlier onset of lactogenesis II (milk production), increased oxytocin release, and increased milk production as a result of frequent SSC are also suggested in the literature (Chen, Nommsen-Rivers, Dewey, & Lonnerdal, 1998; Cong et al., 2015; Gordan, 2015; Hemachandra, Puapornpong, Ketsuwan, & Imchit, 2016). Frequent SSC between mother and baby should be encouraged throughout the postpartum hospital stay and after discharge to home. Infants should be undressed (diaper only) and placed directly on the mother's bare chest. Mother and baby should then be covered with a blanket with the infant's head exposed.

Maternal–Infant Separation Only When Medically Necessary

Healthcare professionals should recommend 10 to 12 feedings at breast per 24-hour period in the first 3 to 5 days after birth. Milk production is the result of lactogenesis I and II. Lactogenesis I begins around the 10th to 22nd week of pregnancy and is hormonally mediated. During lactogenesis I, growth of glandular tissue occurs, and the mammary secretory cells, lactocytes, are formed. Lactogenesis II, the onset of milk production, begins with the separation of the placenta from the uterus at birth, which results in a drop in mother's serum progesterone. Lactogenesis II depends on frequent suckling at the breast. When the infant suckles at the breast, prolactin is released from the mother's anterior pituitary gland, and oxytocin is released from the posterior pituitary gland. Prolactin is responsible for milk production in the mammary gland, and oxytocin is responsible for the milk ejection reflex, which allows the release of the milk from the mammary gland to the milk ducts (Wambach & Riordan, 2016).

The longer the infant is separated from the mother in the hospital, the less opportunity for breastfeeding occurs. In the first few days after birth, several attempts at latching at the breast may be necessary before a good sustained latch is achieved; therefore, mothers need uninterrupted time together with their infants to learn to identify hunger cues and have adequate practice and assistance with breastfeeding. Parents need to be educated in the identification of their infant's hunger cues and to offer the breast when the infant expresses early rather than late hunger cues. Early hunger cues include movement of arms and legs, rooting, lip smacking, and fingers or fist to mouth movement. Early hunger cues may occur while the infant is in a light sleep state with eyes closed. Later hunger cues include restlessness, intermittent or full cry, and inconsolable screaming (Wambach & Riordan, 2016).

Mothers should be encouraged to room in (keep their infants with them continuously through the day and night) to promote quicker response to hunger cues and identification of infant needs. Infant assessments by all providers can and should occur in the mother's hospital room rather than in the nursery. Increased maternal sleep or perceived rest has not been substantiated in the literature when infants are separated from the mother or sent to the nursery (Doan, Gardiner, Gay, & Lee, 2007; Keefe, 1987, 1988; Waldenström & Swenson, 1991). The breastfeeding mother–infant dyad should only be separated when medically necessary.

Pacifier Use

Pacifier use in the healthy term breastfed infant is a somewhat controversial topic. Pacifier use has been associated with shorter breastfeeding duration (Howard et al., 2003; Nelson, Yu, & Williams, 2005) and decreased exclusive breastfeeding (Vogel, Hutchison, & Mitchell, 2001). Long-term pacifier use beyond 6 months of age has been associated with increased risk of otitis media (Niemelä, Pihakari, Pokka, & Uhari, 2000) and dental malocclusion (Peres, Barros, Peres, & Victora, 2007). WHO and UNICEF (2018) through the *Ten Steps to Successful Breastfeeding* recommend educating parents on the possible risks of pacifier use.

However, the AAP has identified pacifier usage to potentially decrease the incidence of SIDS (Hauck, Omojokun, & Siadaty, 2005; Li et al., 2006) and serve as a method of effective pain control in combination with sucrose for infants undergoing painful procedures, for example, heelsticks or circumcision (Stevens, Yamada, & Ohlsson, 2010). The specific recommendations of the AAP regarding pacifier use and breastfeeding infants are to avoid pacifier use in the neonatal period until breastfeeding is well established. The AAP encourages pacifier use in infants undergoing painful procedures and during nap and sleep times as a potential protection against SIDS (Eidelman & Schanler, 2012). One further recommendation is to discourage the use of pacifiers to rule out hunger or delay a feeding; breastfeeding should occur before offering a pacifier. Parents must be educated on all the risks and benefits of pacifier use in the breastfed infant, so they can make an informed decision that best suits their needs and parenting philosophy.

Adequacy of Breastfeeding

The three main indicators of adequate breast milk transfer are audible swallowing by the infant, adequate urine and stool output, and weight gain. All healthcare professionals who care for breastfeeding mother–infant dyads in the neonatal period must demonstrate competence in assessing an adequate transfer of breast milk. At least one complete breastfeed from latch to satiety should be observed, preferably once per shift after birth, but at least once before discharge. Mothers need education on positioning the infant during breastfeeding and on how to achieve a deep latch. The football hold, cross-cradle hold, and the side-lying position are common ways to hold the infant to promote a deep latch. The mother should be taught to support the infant's head with one hand and her breast with the other hand during latching. The mother should hold her breast so that her fingers do not cover her areola. The mother should be taught to hand-express drops of breast milk from her nipple and place on the infant's lips to entice a wide mouth gape. Once the infant has a wide mouth gape, it should be brought quickly to the breast. The infant needs to feel the nipple on its palate to elicit the sucking reflex. The infant should take in most of the mother's areola, and lips should be flanged on the breast.

Once latched and sucking, the healthcare provider should listen for audible swallowing by the infant. In the first few days of breastfeeding, the infant will take 5 to 10 sucks before a swallow will be heard as a soft "k" sound. As the mother's milk begins to come in, swallowing will become more frequent and more audible. An adequate breastfeed is sustained sucking and swallowing for at least 10 to 15 minutes on at least one breast. If the infant detaches from the first breast, the mother can continue feeding on the other breast. Encourage the mother to alternate which breast she starts on with each feeding. Length of feedings in minutes is a less important measure of adequate breastfeeding than sustained audible swallowing followed by signs of satiety, including slowing of sucking, falling asleep, and self-detaching (Wambach & Riordan, 2016). Several breastfeeding assessment tools have been developed and tested in an effort to measure the adequacy of breastfeeding in the early days after birth. The LATCH assessment tool by Jensen, Wallace, and Kelsay (1994) is one such tool that evaluates five different indicators of breastfeeding adequacy (Table 5.3). Each assessment is scored from 0 to 10, with a higher score indicating

TABLE 5.3

LATCH BREASTFEEDING ASSESSMENT TOOL

	0	1	2
Latch	Too sleepy or reluctant No latch achieved	Repeated attempts Hold nipple in mouth Stimulate suck	Grasps breast Tongue down Lips flanged Rhythmic sucking
Audible swallowing	None	A few with stimulation	Spontaneous and intermittent <24 hours old Spontaneous and frequent more than 24 hours old
Type of nipple	Inverted	Flat	Everted (with stimulation)
Comfort of mother	Engorged Cracked/ bleeding/ large blisters or bruises Severe discomfort	Filling Reddened/ small blisters or bruises Mild/ moderate discomfort	Soft Nontender
Hold or positioning	Full assist (staff holds infant at breast)	Minimal assist Teach one side; mother does other Staff holds and then mother takes over	No assist from staff Mother able to position/hold infant

Source: From Jensen, D., Wallace, S., & Kelsay, P. (1994). LATCH: A breastfeeding charting system and documentation tool. *Journal of Obstetric, Gynecologic, and Neonatal Nursing, 23*, 27–32. doi:10.1111/j.1552-6909.1994.tb01847.x

adequate latch and transfer of milk as well as relative comfort of the mother.

The second indicator of adequate breastfeeding is the amount of urine and stool output. Breastfed infants should have one wet diaper the first day of life and increase by one wet diaper for each day of life up to five to six wet diapers per day. Diapers should feel heavier when wet rather than just damp. The urine should be light in color and have slight to no odor. It is normal for breastfed neonates to have reddish colored urine in the first few days of life and this is not an indicator of dehydration (Kernerman & Newman, 2009). Neonates should have at least one stool on the first and second days of life that is green to black and a tarry consistency. By the third and fourth day of life, the neonate should have one to three stools per day that begin to change to a green looser stool as the mother's milk begins to come in. By the fourth to seventh days of life, the neonate should have one to four stools per day that are yellow, loose, and seedy in consistency. By the end of the second week of life, the neonate should have three to five stools per day that are the same consistency, but the volume of the stool will increase as the volume of milk intake from the mother increases. It can be normal for infants to have no stool on an occasional day (Wambach & Riordan, 2016). If a neonate does not have adequate output as previously described, the healthcare professional should assess a breastfeeding for adequate transfer of milk and frequency of breastfeedings and assess the neonate for jaundice and signs and symptoms of dehydration. Healthcare professionals should refer mothers to a lactation consultant for breastfeeding difficulties.

The third indicator of adequate breastfeeding is weight gain. Some weight loss is expected in the healthy term neonate. A weight loss up to 5% of birth weight in the first 3 days is considered normal and can be partially attributed to evaporative loss after birth. At 7% weight loss, the healthcare provider should assess breastfeeding as previously described and also assess urine and stool output. **Emergency Alert: A neonate with a greater than 7% weight loss who is having adequate breastfeeding and output could have been fluid overloaded as a result of large quantities of intravenous fluids given to the mother during labor** (Lawrence & Lawrence, 2015). If a 10% weight loss occurs in the first 3 days of life, intervention is necessary to assist the mother's body with lactogenesis II and to assist the baby in adequate transfer of milk. Mothers should be educated and encouraged to pump both breasts after a feeding with a hospital-grade breast pump for 10 to 15 minutes at least eight times per day. This will provide extra stimulation and assist with onset of milk. The mother should feed any expressed breast milk to the baby via cup, finger feeding, or at breast using a Supplemental Nursing System™, or a feeding tube inserted at the corner of the infant's mouth while nursing. Mothers and support persons must be educated by a nurse or a lactation consultant on safety and use of supplemental feeding methods.

If the mother is unable to pump adequate volumes of breast milk, the neonate's urine and stool output is not adequate, and the baby is unable to consistently transfer milk from the breast, then supplementation with formula may be necessary. Formula supplementation in the first 24 to 48 hours after birth should be limited to 10 to 15 mL per feeding given after a breastfeeding attempt (Wambach & Riordan, 2016). At greater than 48 hours of birth, formula supplementation should be limited to 30 mL per feeding and should be given after breastfeeding attempts. Supplementation should only continue until mother's milk is established.

Breastfeeding Follow-Up After Discharge

Breastfed neonates should be seen by a healthcare provider within 3 to 5 days after discharge from the hospital stay to assess breastfeeding adequacy, the onset of mother's milk, presence of jaundice or elevated bilirubin levels, and weight gain. Neonates with weight loss should gain back to birth weight by 14 days of age. Breastfeeding should be assessed at all subsequent infant healthcare provider visits to include not only the baby's health and growth, but also the mother's support systems and motivation to continue breastfeeding. Exclusive breastfeeding should be encouraged and promoted throughout the first six months of the infant's life with continued breastfeeding and addition of solid foods through the first year of life and beyond if mother and infant desire. Formula supplementation should be avoided unless medically indicated.

Formula Feeding

If a mother chooses not to breastfeed or breastfeeding is contraindicated (maternal infection with HIV, active TB, human T-cell lymphotropic virus, untreated brucellosis, or treatment with chemotherapeutic agents) and banked milk is not available or feasible, then formula feeding is the most available alternative (Eidelman & Schanler, 2012). Commercially prepared cow's milk-based formulas are all relatively similar in their composition of nutrients, vitamins, minerals, proteins, carbohydrates, and fat. Three other types of formula are soy-based formulas, casein or whey-hydrolysate formulas, and amino acid formulas. Soy formulas are generally recommended to mothers whose infants have a cow's milk intolerance, galactosemia, and hereditary lactase deficiency. Casein or whey-hydrolysate formulas are recommended to children who cannot tolerate cow's milk or soy-based formulas.

Formulas come in many forms and concentrations, for example, concentrate, ready to feed, or powder. Parents and caregivers need to be educated on how to prepare the formula correctly according to product package instructions. Improperly prepared formula can lead to infant malnutrition, electrolyte imbalance, and even death (Walker, 1993). Formula or breast milk should never be heated in a microwave because of uneven heating and the potential for burns. Energy requirements for normal growth and activity of infants is approximately 108 kcal/kg/day from birth to 6 months of age and approximately 98 kcal/kg/day from 6 to 12 months of age (Kleinman, 2008). Newborns receiving formula should be fed 1 to 2 oz per feeding every 3 to 4 hours for the first week, and advanced to 2 to 4 oz per feeding around 1 week of age. A general volume recommendation is 2.5 oz/lb per day. For example, a 10-lb baby would receive 25 oz of formula per day divided into approximately six to eight feedings (every 3–4 hours) of 3 to 4 oz per bottle (Blum-Kemelor & Leonberg, 2009). Prepared formula cannot sit at room temperature for more than 2 hours. After 2 hours at room temperature, bacteria growth begins to proliferate (WHO, 2007). Any formula that the baby does not consume from a bottle should be thrown away and not refrigerated. Prepared formula can be refrigerated for 24 hours prior to consumption.

DISCHARGE SCREENING

Hearing Screening

Hearing loss is one of the most common congenital anomalies, occurring in approximately 2 to 4 infants per 1,000 (American Speech-Language-Hearing Association, 2018; Delaney et al., 2012). Prior to implementation of universal newborn screening (NBS), testing was only done on infants who met the criteria of the high-risk register. Unfortunately, about 50% of infants born with hearing loss have no known risk factors (American Speech-Language-Hearing Association, 2018; Delaney et al., 2012).

The ability to hear during the first few years of life is critical for the development of speech, language, and cognition. Early identification and intervention can prevent severe psychosocial,

educational, and linguistic repercussions. Infants with hearing loss who are not identified by 6 months of age will likely have delays in speech and language development. Intervention at or before 6 months of age promotes the ability of a child with hearing loss to develop normal speech and language development (Delaney et al., 2012).

The two methods used in most universal hearing-screening programs are the otoacoustic emissions (OAEs) and automated auditory brainstem response (AABR). OAEs are used to assess cochlear integrity and are physiologic measurements of the response of the outer hair cells to acoustic stimuli. When using the OAE method, a probe is placed in the ear canal and click stimuli are delivered causing the OAEs to be generated by the cochlea, which are then measured with a microphone (American Speech-Language-Hearing Association, 2018; Delaney et al., 2012). The presence of the OAE responses indicates that hearing is in the normal to near-normal range.

AABR is an electrophysiologic measurement that is used to assess auditory function from the eighth nerve through the auditory brainstem (Delaney et al., 2012). This is done by placing disposable electrodes high on the forehead, on the mastoid, and on the nape of the neck. The click stimulus is delivered to the infant's ear with small disposable earphones. Most AABR systems compare an infant's waveform with a control that was developed from normal ABR infant data (American Speech-Language-Hearing Association, 2018; Delaney et al., 2012). A pass or fail response is determined from this comparison. Infants who do not pass the universal hearing screening at birth should have follow-up testing within 1 month. This follow-up appointment allows for additional testing and medical diagnosis.

Newborn Screening

NBS tests the newborn for many hormonal, genetic, and metabolic disorders. This screening is done with a simple blood test that allows for early detection of preventable life-threatening disorders. There are 31 disorders that have been identified for routine screening. Current standards are determined at the state level, and most states screen for the majority of the recommended disorders, though there is some variation from state to state on the specific disorders tested (CDC, 2016b; National Newborn Screening and Genetic Resource Center, 2014).

Without proper screening and treatment, infants and children can suffer mental retardation, physical disability, or even death. With early treatment shortly after birth, many affected infants and children can lead normal healthy lives (AWHONN, 2011). There is a need for the development of national standards to ensure that all states screen for all of the recommended disorders.

In April 2008, the Newborn Screening Saves Lives Act (Public Law 110–204, 2008) was signed into law, but this law recommends rather than mandates states to increase the number of disorders they test for.

In 1999, the AAP developed a task force that recommended greater uniformity among states. In response, the American College of Medical Genetics issued guidelines for state NBS programs that recommended all states test for a core panel of 29 disorders (AAP Newborn Screening Authoring Committee, 2008). Then, in 2010, the Advisory Committee for Heritable Disorders in Newborns and Children agreed to include severe combined immunodeficiency in the panel (AWHONN, 2011). The following is a complete list of the disorders:

Organic acid metabolism disorders

- Isovaleric acidemia
- Glutaric acidemia
- 3-OH 3-CH3 glutaric aciduria
- Multiple carboxylase deficiency
- Methylmalonic acidemia due to mutase deficiency
- Methylmalonic acidemia (Cbl A, B)
- 3-Methylcrotonyl-CoA carboxylase deficiency
- Propionic acidemia
- Beta-ketothiolase deficiency

Fatty acid oxidation disorders

- Medium chain acyl CoA dehydrogenase
- Very long chain acyl CoA dehydrogenase deficiency
- Long chain l-3-OH acyl CoA dehydrogenase deficiency
- Trifunctional protein deficiency
- Carnitine uptake defect

Amino acid metabolism disorders

- Phenylketonuria
- Maple syrup urine disease
- Homocystinuria due to cystathionine beta synthase (CBS) deficiency
- Citrullinemia
- Argininosuccinic acidemia
- Tyrosinemia type 1

Hemoglobinopathies

- Sickle cell anemia (Hb SS)
- Hemoglobin S/beta-thalassemia (Hb S/Th)
- Hemoglobin S/C (Hb S/C)

Others

- Congenital hypothyroidism
- Biotinidase deficiency
- Congenital adrenal hyperplasia due to 21-hydroxylase deficiency
- Classic galactosemia
- Hearing loss
- Cystic fibrosis
- Severe combined immunodeficiency

March of Dimes Foundation developed a recommendation for all states to test for these 30 conditions, grouping them into five categories:

- Amino acid metabolism disorders
- Organic acid metabolism disorders
- Fatty acid oxidation disorders
- Hemoglobinopathies
- Others, please see https://www.marchofdimes.org/baby/newborn-screening-tests-for-your-baby.aspx for more specific information

All states collect blood samples from newborns during their birth hospitalization; these samples are usually referred to as blood spots (see Figure 5.3). Some states discard the blood samples when the NBS is complete, and others store the blood spots for future research. Genetic privacy, parental consent, and security must be incorporated into any blood storage system and there needs to be a mechanism in place that addresses parents' rights with regard to storage and future uses with the blood spots (AWHONN, 2011).

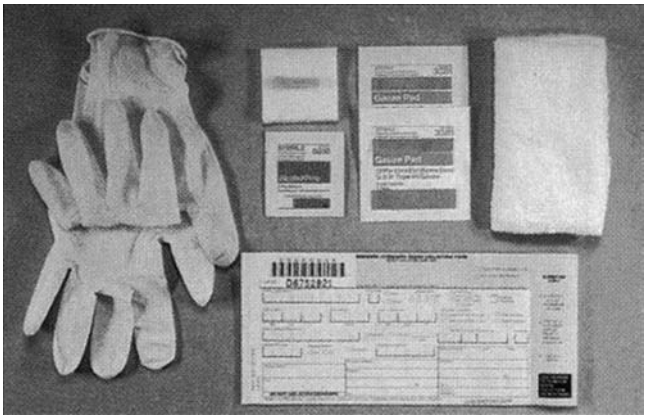
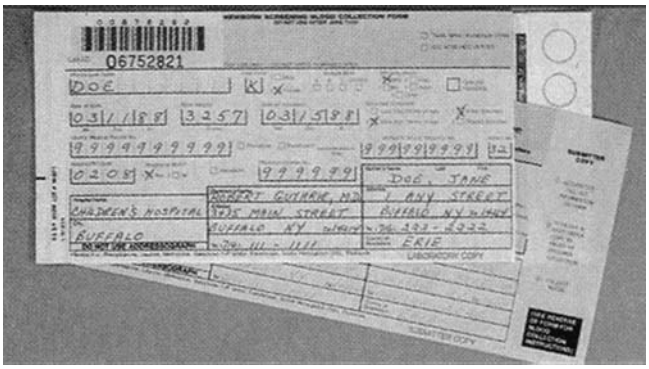
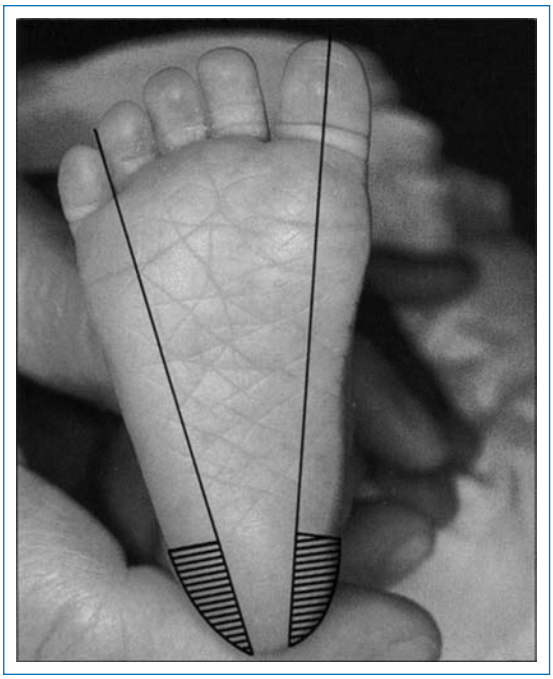


FIGURE 5.3 Newborn screen blood specimen collection and handling procedure.

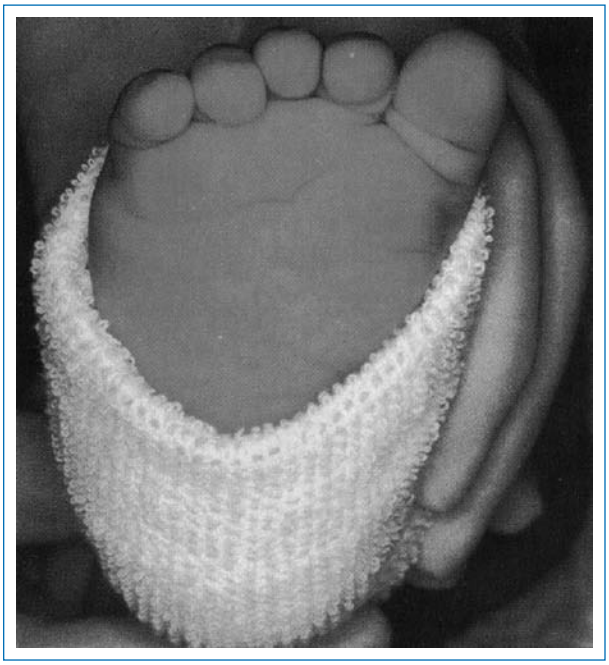
1. Equipment: Sterile lancet with tip less than 2.4 mm, sterile alcohol prep, sterile gauze pads, soft cloth, blood collection form, gloves.



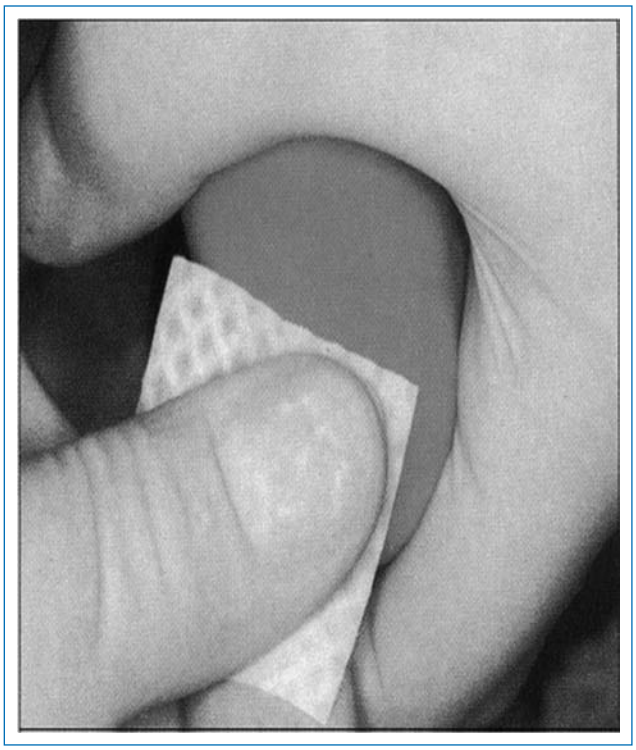
2. Complete all information. Do not contaminate filter paper circles by allowing the circles to come in contact with spillage or by touching before or after blood collection.



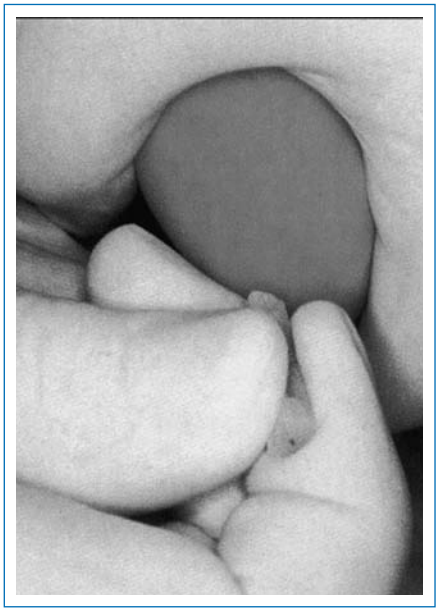
3. Hatched area indicates safe areas for puncture site.



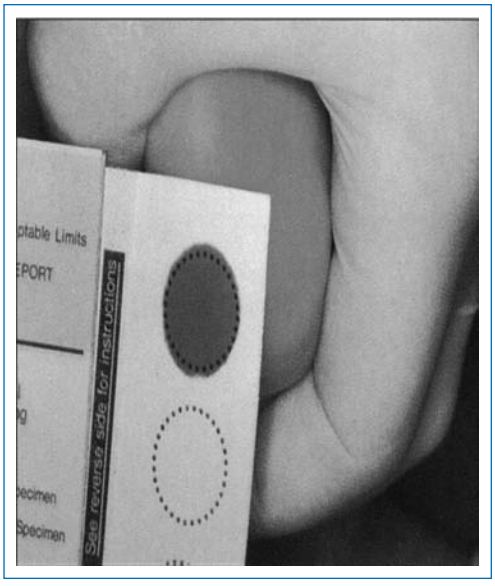
4. Warm site with soft cloth, moistened with warm water or a heel warmer for 3 to 5 minutes.



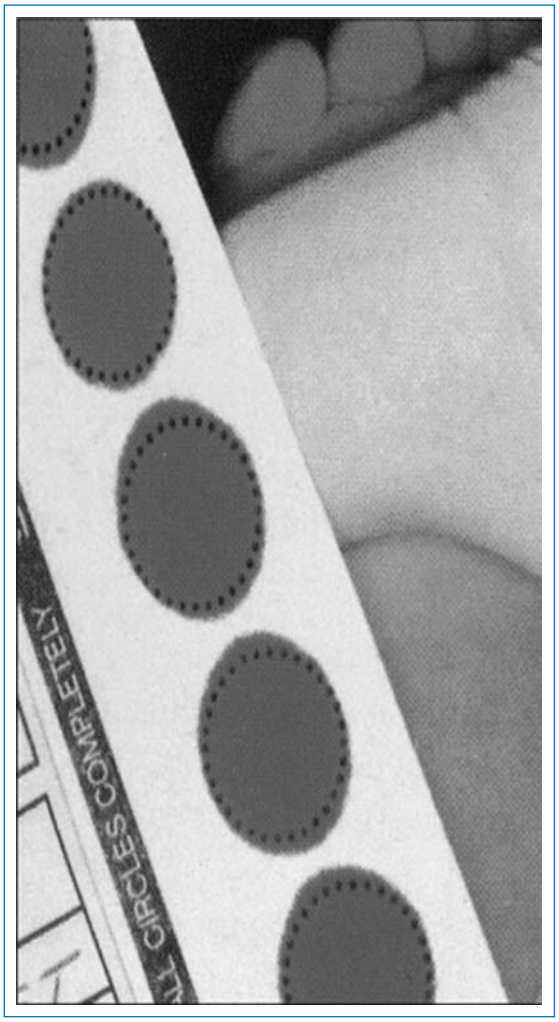
5. Cleanse site with alcohol prep. Wipe dry with sterile gauze pad.



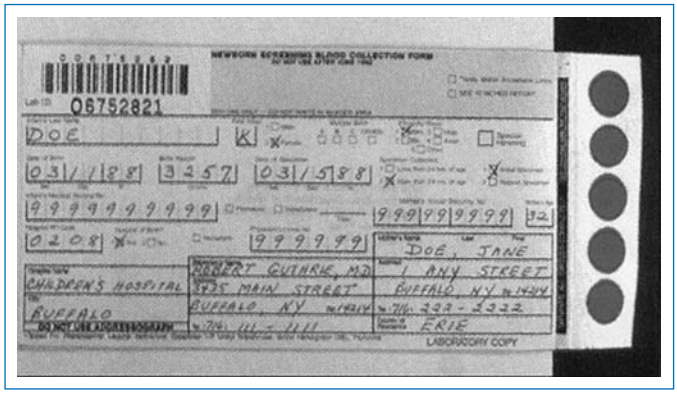
6. Puncture heel. Wipe away first blood drop with sterile gauze pad. Allow another large blood drop to form.



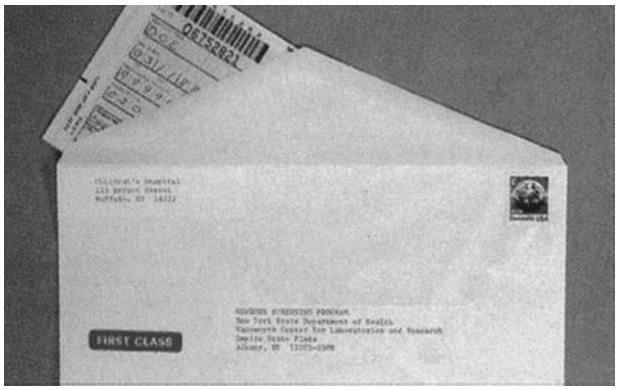
7. Lightly touch filter paper to large blood drop. Allow blood to soak through and completely fill circle with single application to large blood drop. (To enhance blood flow, very gentle intermittent pressure may be applied to area surrounding puncture site.) Apply blood to one side of filter paper only.



8. Fill remaining circles in the same manner as in step 7, with successive blood drops. If blood flow is diminished, repeat steps 5 through 7. Care of skin puncture site should be consistent with your institution's procedures.



9. Dry blood spots on a dry, clean, flat nonabsorbent surface for a minimum of 4 hours.



10. Mail completed form to testing laboratory within 24 hours of collection.

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CRITICAL CONGENITAL HEART DISEASE SCREENING

Pulse oximetry screening (POS) of the newborn is an effective, noninvasive, and inexpensive tool that is beneficial in detecting critical congenital heart disease (cCHD) in newborns (Riede et al., 2010). Congenital heart defects are the most common serious birth defects, affecting approximately 8 of every 1,000 newborns, and cCHDs affect 2 to 3 per 1,000 live births. The seven defects classified as cCHDs are hypoplastic left heart syndrome, pulmonary atresia (with intact septum), tetralogy of Fallot, total anomalous pulmonary venous return, transposition of the great arteries, tricuspid atresia, and truncus arteriosus. Babies with one of these cCHDs are at significant risk for death or disability if their heart defect is not diagnosed and treated soon after birth. These seven cCHDs potentially can be detected using POS, which is a test to determine the amount of oxygen in the blood and pulse rate. Certain hospitals routinely screen all newborns using POS. However, POS is not currently included in NBS in most states (AAP, 2018; CDC, 2018). Prenatal ultrasound and physical examination alone

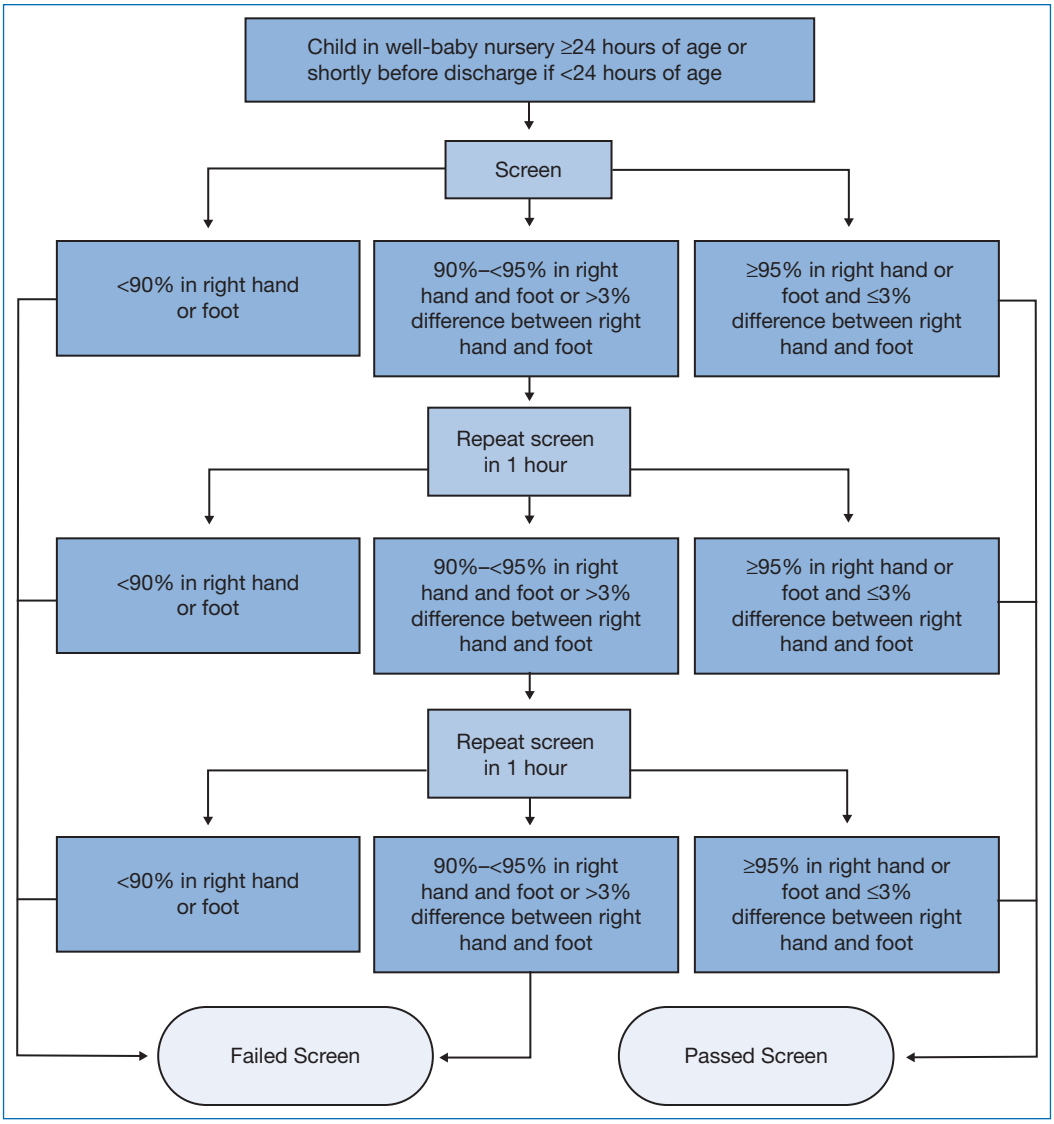

FIGURE 5.4 Newborn screening algorithm for critical congenital heart defects.

Note: Percentages refer to oxygen saturation as measured by pulse oximeter.

Source: Centers for Disease Control and Prevention. (2018). *Congenital heart defects information for healthcare providers.* Retrieved from https://www.cdc.gov/ncbddd/heartdefects/hcp.html

can miss cCHDs because symptoms may not appear until after discharge when the ductus arteriosus closes. Heart murmurs may be absent or misleading due to underlying anatomy, prolonged decline of pulmonary vascular resistance, or reduced ventricular function (Riede et al., 2010). Diagnosis may be further complicated by trends to discharge early. It has been estimated that at least 280 infants with an unrecognized cCHD are discharged each year from newborn nurseries in the United States (CDC, 2018). These babies are at risk for having serious problems within the first few days or weeks of life and often require emergency care.

The first signs of acute cCHD may be circulatory collapse requiring the need for cardiopulmonary resuscitation or death. Delays in diagnosis have been associated with significant morbidity and mortality. The current incidence of serious compromise resulting in undiagnosed cCHD has been estimated to be 1 per 15,000 to 1 per 26,000 live births (Riede et al., 2010). These data have led to a broad consensus that screening for cCHD is warranted.

Pulse oximetry can detect mild hypoxemia, which is a sign for many types of cCHD that may not be recognized by physical examination. This was first reported in 1995, and since then many studies have shown that screening with pulse oximetry is an effective tool for the detection of cCHD (Riede et al., 2010). Once identified, babies with a cCHD can be seen by cardiologists and can receive specialized care and treatment that could prevent death or disability early in life. Treatment can include medications and/or surgery.

When to Screen

Screening is done when a baby is 24 to 48 hours of age. If the baby is to be discharged from the hospital before he or she is 24 hours of age, screening should be done as late as possible before discharge. If the results are "negative" (in-range result), it means that the baby's test results did not show signs of a cCHD. This type of screening test does not detect all cCHDs, so it is possible to still have a critical or other heart defect with a negative screening result. If the results are "positive" (out-of-range result), it means that the baby's test results showed low levels of oxygen in the blood. This can be a sign of a cCHD. This does not always mean that the baby has a cCHD. It just means that more testing such as an echocardiogram is needed. The algorithm in Figure 5.4 shows the steps on how to complete the screening.

A screen is considered positive if (1) any oxygen saturation measure is less than 90% (in the initial screen or in repeat screens); (2) oxygen saturation is less than 95% in the right hand and foot on three measures, each separated by 1 hour; or (3) a greater than 3% absolute difference exists in oxygen saturation between the right hand and foot on three measures, each separated by 1 hour. Any screening that is less than or equal to 95% in the right hand or foot with a less than or equal to 3% absolute difference in oxygen saturation between the right hand or foot is considered a negative screen, and screening would end.

Any infant with a positive screen should have a diagnostic echocardiogram, which would involve an echocardiogram within the hospital or birthing center, transport to another institution for the procedure, or use of telemedicine for remote evaluation. The infant's healthcare provider should be notified immediately, and the infant might need to be seen by a cardiologist for follow-up.

False positives are decreased if the infant is alert, and timing cCHD screening around the time of the newborn hearing screening improves efficiency. POS should not replace taking a complete family medical and pregnancy history and completing a physical examination, which sometimes can detect cCHD before the development of hypoxia.

DISCHARGE

Planning for discharge should begin at the time of admission. Every interaction with the parents should be a teaching moment. Discharge instructions for the parents should be given by both the nurse caring for the newborn and the primary care provider and should include early follow-up appointment with the pediatrician or primary care provider within 72 hours of discharge from the birth hospitalization, feeding schedules, routine bathing, home care needs, umbilical cord care, signs and symptoms of infection, when to call your primary care provider, voiding and stooling patterns, and infant safety.

SUMMARY

This chapter has outlined the basic information for assessing, managing, and discharging the normal newborn. There is growing evidence to support the need for neonatal nurses to have a better understanding of the normal newborn as they care for the sick and/or preterm infant.

CASE STUDY

■ **Identification of the Problem.** A term male infant presented at birth with 2 to 5 mm pustules covering his face, chest, trunk, and scrotum.

■ **Assessment: History and Physical Examination.** A term male infant, 39 + 4 weeks' gestation, weighing 3.6 kg, was born via a cesarean section for failure to progress. Apgars were 8 and 9 at 1 and 5 minutes, respectively. The mother was a 33-year-old G1 P0. The pregnancy was uncomplicated, mother's blood type is A+, syphilis screen was negative, hepatitis screen was negative, HIV screen was negative, and Rubella was immune. Group B strep culture was negative. Mother received prenatal care. Medications during the pregnancy included prenatal vitamins. Complications during labor included failure to progress, requiring a cesarean section.

■ **Physical Examination on Admission to the Newborn Nursery**

- General: AGA term male infant in no distress with pustules covering his body. On admission to the newborn nursery, the infant was placed on a radiant warmer. Vital signs were stable: temperature 98.2°F, heart rate 158, respirations 48, blood pressure 72/48 mmHg, $m = 52$; blood sugar was 86.
- HEENT: mild caput, anterior fontanelle soft and flat, sutures approximated and mobile, palate intact, and ears appropriately placed; eyes normally spaced with red reflex bilaterally, pupils reactive, no hemorrhage noted. Ears with ready recoil and symmetric
- RESP: bilateral breath sounds clear and equal, no grunting or retractions
- CV: regular rate and rhythm, good perfusion, brisk cap refill, normal pulses × 4 extremities, and no murmur
- ABDOMEN: soft, flat, and nontender. Active bowel sounds and no hepatomegaly
- GU: normal male genitalia, testes descended bilaterally, rugae present, and anus patent
- NEURO: awake and active, tone AGA. Good suck and gag reflex

- SPINE: spine straight and intact, no dimple and neck supple, no masses
- EXTREMITIES: moving all extremities well with symmetric extremities; no hip clicks or clunks
- SKIN: warm and dry. Moderate nonerythematous pustule approximately between 1 and 4 mm on the face, chest, trunk, scrotum, and thighs. Vesicle appears to contain milky, purulent exudate. The pustules rupture easily. Some appear superficial and wiped off easily with vernix.

■ Differential Diagnosis

- Acropustulosis
- Candidiasis
- Erythema toxicum
- Herpes simplex virus infection
- Milia
- Miliaria
- Neonatal pustular melanosis
- *Staphylococcus aureus* infection

■ **Diagnostic Tests.** If the appearance is typical of transient neonatal pustular melanosis, no further workup is indicated. If appearance is not typical, potassium hydroxide preparation, Gram stain, and Wright-Giemsa stain can be obtained to support other diagnoses in the differential. Bacterial and viral cultures can be done from the pustule. If there is a clustering of pustules, a polymerase chain reaction to identify possible herpes simplex should be considered.

■ **Working Diagnosis.** Transient neonatal pustular melanosis.

This is a benign, self-limiting rash of unknown etiology. In the United States, incidence has been reported to be 2.2% in white infants and as high as 4.4% in black infants and infants with darker pigmentation.

The rash starts in utero, so eruptions are always present at birth but the clinical appearance can vary. At first, the pustules appear as uniform, round, 2- to 4-mm nonerythematous pustules that rupture easily. There is a thin white scale that is left around the perimeter of each denuded pustule. After a few hours, a central pigmented brown macule appears. This is smooth and has distinct borders that look like a freckle. The hallmark of this rash is the hyperpigmented spot that remains after the pustule has resolved. They may be profuse or sparse and typically are found under the chin and on the neck, upper chest, back, and buttocks. Occasionally, the palms, soles, and scalp are affected.

■ **Management.** No treatment is indicated. Parents will be anxious when they see pustules covering their baby and will need reassurance that neonatal pustular melanosis is a benign finding and that it fades and disappears over a period of months.

EVIDENCE-BASED PRACTICE BOX

Early SSC in the Healthy Term Newborn

SSC between mother and baby at birth has been associated with numerous physiologic and psychological benefits, including temperature, heart rate, and respiratory rate stabilization of the newborn, less crying, decreased pain with procedures, and less incidence of hypoglycemia in the newborn (Bergman, Linley, & Fawcus, 2004; Christensson et al., 1992; Christensson, Cabrera, Christensson, Unvas Moberg, & Winberg, 1995; Johnston et al., 2014; Nolan & Lawrence, 2009). Breastfeeding initiation and duration is also positively impacted by SSC. Mothers who engaged in SSC with their newborns at birth were more likely to have a successful breastfeed, post birth, than mothers who did not engage in SSC (Carfoot, Williamson, & Dickson, 2004, 2005; Karimi & Khadivzadeh, 2012). Mothers who engaged in SSC were also more likely to be exclusively breastfeeding at 6 weeks, 3 and 6 months post birth (Anderson et al., 2009; Gouchon et al., 2010; Sharma, 2016; Vaidya, Sharma, & Dhungel, 2005). Mothers who engage in SSC also have reported less pain (Nolan & Lawrence, 2009; Wagner, Lawrence, Xu, & Melsom, 2018), state less anxiety 3 days post birth (Shiau, 1997), report higher self-efficacy with breastfeeding at 1 month post birth (Aghdas, Talat, & Sepideh, 2014), and report less postpartum depressive symptoms and physiologic stress (Bigelow, Power, MacLellan-Peters, Alex, & McDonald, 2012).

Moore, Bergman, Anderson, and Medley (2016) conducted a meta-analysis of 46 randomized controlled trials regarding SSC and concluded that women who experienced SSC were significantly more likely to be breastfeeding at 1 to 4 months after birth, and were more likely to exclusively breastfeed than women who did not experience SSC. Moore et al. (2016) also found that infants who experienced SSC had greater stability of the cardiorespiratory system and higher glucose levels than infants who did not experience SSC. The authors found no significant difference in infant temperature between infants who did or did not experience SSC. Johnston et al. (2014) conducted a meta-analysis of 25 randomized controlled trials regarding SSC and procedural pain. The authors found that infants who received SSC during painful procedures had less crying and lower heart rate than infants who did not receive SSC.

The AAP Policy Statement (2012), the Academy of Breastfeeding Medicine (2010), the AWHONN (Dabrowski, 2007), and the BFHI (2018) all have position statements and recommendations for policy regarding the implementation of SSC at birth. All healthy term infants are recommended to be placed skin to skin immediately after delivery for at least 1 hour. Newborns should be placed naked or with diaper only, and prone on the mother's chest. Mother and baby should be covered with a warm blanket. From this position, the infant can be dried, Apgar scores assigned, initial assessment completed, and identification bracelets placed on mother and newborn. Newborn care and measurements/weight and length, including bathing, vitamin K, and erythromycin administration, should be delayed to allow uninterrupted SSC and optimal opportunity for the initial breastfeed within the first hour after birth.

Stevens, Schmied, Burns, and Dahlen (2014) conducted a review of the literature on SSC in the operating room (OR) after cesarean delivery. The authors not only concluded, based on the literature, that SSC in the OR with healthy term newborns was feasible, but also that SSC in the OR promotes breastfeeding initiation, reduced formula supplementation in the hospital, increased bonding and maternal satisfaction, promoted more stable temperature, and reduced newborn stress. While the evidence for SSC is strong, barriers to implementation do exist. Haxton, Doering, Gingras, and Kelly (2012) discussed challenges including overcoming staff concerns, modifying unit order sets, and adapting electronic medical records to allow for documentation

(*continued*)

EVIDENCE-BASED PRACTICE BOX (*continued*)

and tracking of SSC. While overcoming these challenges took time and coordination, the authors express that the outcome of increasing breastfeeding initiation rates from 74% to 84% within a 6-month time frame was worth their effort.

While SSC has been safely implemented in hospitals across the United States and the world, some rare adverse events have been documented. Andres et al. (2011) reviewed six cases of apparent life-threatening events (ALTEs) that occurred with infants in SSC within two hours after birth. In all six cases, the ALTE occurred with no apparent cause, and all six infants were born at term and were otherwise healthy. The common risk factors identified among the six cases were that the mothers were primiparous, in SSC with the infant in a prone position on the mother's chest, and the mother and infant were left alone in the delivery room. To improve safe SSC practice, Feldman-Winter and Goldsmith (2016) suggest that continuous observation by staff and obtaining frequent vital signs of the newborn occur throughout SSC. The authors also suggest safe positioning of the newborn during SSC including making sure the infant's face is visible with mouth and nose not covered and the infant's head in the sniffing position and turned to one side with a straight neck. The infant's shoulders and chest should face the mother and the infant's legs should be flexed.

References

Academy of Breastfeeding Medicine. (2010). *Clinical protocol #7: Model breastfeeding policy*. Retrieved from http://www.bfmed.org/Resources/Protocols.aspx

Aghdas, K., Talat, K., & Sepideh, B. (2014). Effect of immediate and continuous mother–infant skin-to-skin contact on breastfeeding self-efficacy of primiparous women: A randomised control trial. *Women and Birth, 27*(1), 37–40. doi:10.1016/j.wombi.2013.09.004

American Academy of Pediatrics. Policy Statement. (2012). Breastfeeding and the use of human milk. *Pediatrics, 129*, e827–e841. doi:10.1542/peds.2011–3552

Anderson, G. C., Chiu, S. H., Dombrowski, M. A., Swinth, J. Y., Albert, J. M., & Wada, N. (2009). Mother-newborn contact in a randomized trial of kangaroo (skin-to-skin) care. *Journal of Obstetric, Gynecologic, and Neonatal Nursing, 32*, 604–611. doi:10.1177/0884217503256616

Andres, V., Garcia, P., Rimet, Y., Nicaise, C., & Simeoni, U. (2011). Apparent life-threatening events in presumably healthy newborns during early skin-to-skin contact. *Pediatrics, 127*(4), e1073–e1076. doi:10.1542/peds.2009-3095

Baby Friendly USA. (2018, June). *Find a baby-friendly facility*. Retrieved from https://www.babyfriendlyusa.org/find-facilities

Bergman, N. J., Linley, L. L., & Fawcus, S. R. (2004). Randomized control trial of skin-to-skin contact from birth versus conventional incubator for physiological stabilization. *Acta Paediatrica, 93*, 779–785. doi:10.1111/j.1651-2227.2004.tb03018.x

Bigelow, A., Power, M., MacLellan-Peters, J., Alex, M., & McDonald, C. (2012). Effect of mother/infant skin-to-skin contact on postpartum depressive symptoms and maternal physiological stress. *Journal of Obstetric, Gynecologic, and Neonatal Nursing, 41*, 369–382. doi:10.1111/j.1552–6909.2012.01350.x

Carfoot, S., Williamson, P. R., & Dickson, R. (2004). The value of a pilot study in breastfeeding research. *Midwifery, 20*, 188–193. doi:10.1016/j.midw.2003.11.002

Carfoot, S., Williamson, P. R., & Dickson, R. (2005). A randomized control trial in the north of England examining the effects of skin-to-skin care on breastfeeding. *Midwifery, 21*, 71–79. doi:10.1016/j.midw.2004.09.002

Christensson, K., Cabrera, T., Christensson, E., Unvas Moberg, K., & Winberg, J. (1995). Separation distress call in the human neonate in the absence of maternal body contact. *Acta Paediatrica, 84*, 468–473. doi:10.1111/j.1651-2227.1995.tb13676.x

Christensson, K. Siles, C., Moreno, L., Belaustequi, A., De La Fuente, P., Lagercrantz, H., . . . Winberg, J. (1992). Temperature, metabolic adaption, and crying in healthy full-term newborns cared for skin-to-skin or in a cot. *Acta Paediatrica, 81*, 488–493. doi:10.1111/j.1651-2227.1992.tb12280.x

Dabrowski, G. A. (2007). Skin-to-skin contact: Giving birth back to mothers and babies. *Nursing for Women's Health, 11*, 64–71. doi:10.1111/j.1751-486X.2007.00119.x

Feldman-Winter, L., Goldsmith, J. P., & Task Force on Sudden Infant Death Syndrome. (2016). Safe sleep and skin-to-skin care in the neonatal period for healthy term newborns. *Pediatrics, 138*(3), e20161889. doi:10.1542/peds.2016-1889

Gouchon, S., Gregori, D., Picotto, A., Patrucco, G., Nangeroni, M., & Di Giulio, P. (2010). Skin-to-skin after cesarean delivery: An experimental study. *Nursing Research, 59*(2), 78–84. doi:10.1097/NNR.0b013e3181d1a8bc

Haxton, D., Doering, J., Gingras, L., & Kelly, L. (2012). Implementing skin-to-skin contact at birth using the Iowa model. *Nursing for Women's Health, 16*, 222–230. doi:10.1111/j.1751–486x.2012.01733.x

Johnston, C., Campbell-Yeo, M., Fernandes, A., Inglis, D., Streiner, D., & Zee, R. (2014). Skin-to-skin care for procedural pain in neonates. *Cochrane Database of Systematic Reviews,* (2) CD008435. doi:10.1002/14651858.CD008435.pub3

Karimi, A., & Khadivzadeh, T. (2012). W149 The effects of mother-infant skin to skin contact on breastfeeding experience. *International Journal of Gynecology and Obstetrics, 119*, S753. https://doi.org/10.1016/s0020-7292(12)61874-8

Moore, E. R., Bergman, N., Anderson, G. C., & Medley, N. (2016). Early skin-to-skin contact for mothers and their healthy newborn infants. *Cochrane Database of Systematic Reviews*, (11), CD003519. doi:10.1002/14651858.CD003519.pub4

Nolan, A., & Lawrence, C. (2009). A pilot study of a nursing intervention protocol to minimize maternal–infant separation after cesarean birth. *Journal of Obstetric, Gynecologic, and Neonatal Nursing, 38*, 430–442. doi:10.1111/j.1552-6909.2009.01039.x

Sharma, A. (2016). Efficacy of early skin-to-skin contact on the rate of exclusive breastfeeding in term neonates: A randomized controlled trial. *African Health Sciences, 16*(3), 790–797. doi:10.4314/ahs.v16i3.20

Shiau, S.-H. H. (1997). *Randomized control trial of kangaroo care with full-term infants: Effects on maternal anxiety, breast milk maturation, breast engorgement, and breastfeeding status* (Doctoral dissertation). Available from Proquest Dissertations and Theses database. (UMI No. 9810943)

Stevens, J., Schmied, V., Burns, E., & Dahlen, H. (2014). Immediate or early skin-to-skin contact after a Caesarean section: A review of the literature. *Maternal and Child Nutrition, 10*(4), 456–473. doi:10.1111/mcn.12128

Vaidya, K., Sharma, A., & Dhungel, S. (2005). Effect of early mother–baby close contact over the duration of exclusive breastfeeding. *Nepal Medical College Journal, 7*, 138–140. Retrieved from https://europepmc.org/abstract/MED/16519083

Wagner, D. L., Lawrence, S., Xu, J., & Melsom, J. (2018). Retrospective chart review of skin-to-skin contact in the operating room and administration of analgesic and anxiolytic medication to women after cesarean birth. Nursing for Women's Health, 22(2), 116–125. doi:10.1016/j.nwh.2018.02.005 to women after cesarean birth. *Nursing for Women's Health, 22*(2), 116–125. doi:10.1016/j.nwh.2018.02.005

PARENT VOICES

Jennifer Canvasser, MSW

My spouse and I struggled with infertility for 3 years before finding out we would be welcoming twins to the world. Despite our planning and best efforts, our twins, Micah and Zachary, were born at 27 weeks' gestation. Zachary spent 91 days in the NICU, while our son Micah was hospitalized for a total of 299 days due to developing NEC. Tragically, Micah died from complications of NEC when the twins were 11 months old.

Three years after Micah and Zachary were born, we welcomed our rainbow baby, Elijah, to the world. Elijah was born weighing almost 9 lb at over 41 weeks' gestation. Thankfully, it was a healthy term pregnancy, yet I was constantly terrified and anxious of giving birth prematurely. It was most helpful when nurses would validate my feelings and recognize them as normal, given my past experience. Writing served as a helpful outlet for me during my pregnancy with Elijah, and I even wrote about it here: www.huffingtonpost.com/entry/5-ways-to-support-a-family-expecting-a-rainbow-baby_b_7222608.html

Number 3 in the blog really stands out for me as a bereaved mother: Get the birth order right. Death does not change birth order, simple as that.

Pregnancy after giving birth prematurely—or after a loss—is unique and these mothers deserve an empathetic, responsive care team tuned in to their needs and experiences.

Heather McKinnis

Our first baby came so early that deciding to give our micropreemie a sibling was a difficult decision. Each of our pregnancies after our preemie was emotionally and physically draining. Progesterone injections, countless ultrasounds, some bedrest, and early full-term scheduled C-sections became our normal. I had panic attacks, anxiety, and nightmares, although these decreased with each pregnancy. We never discovered the reason my first son came so early and each pregnancy was filled with the unknown. In the end, we were able to deliver three more beautiful babies close to full term. I was able to experience their deliveries, hear their cries, breastfeed, and hold them skin to skin. I finally felt like I was able to experience motherhood like everyone else around me. All those moments that my son's extremely premature delivery stole from us were given back three times over and I'll be forever grateful. After everything we went through with our 25-weeker, these experiences were incredibly healing.

Tracy Pella

We gave birth to our twins at 23 + 4 weeks and one of our sons passed away the same day and our other son spent 134 days in the NICU. Post-NICU was filled with very much a "23-weeker life," including appointments, medications, and isolation. When our surviving twin was 4 years old, we were blessed to give birth to our daughter at 37 weeks during a planned C-section. Her birth may have been "normal" by standards of the baby world, but it was far from our normal. Remember, our normal was the 23-weeker life. Our first birth included saying goodbye to one of our sons and watching the other fight for his life for several months. That was our normal!

Being able to plan her arrival and the anticipation was exhausting. I often found myself waiting for the floor to drop from under me. It was almost like we wouldn't allow ourselves to believe we could have a normal delivery. Anxiety took over when I realized she wouldn't be monitored 24/7. I understood she was healthy, but it was more natural to think we wouldn't be able to take her home with us. Visitor after visitor commented that we must be elated she arrived full-term and healthy. Yes, we were happy, but we needed everyone to understand that this was new territory for us. We had put our defenses up and we had to get used to the idea that we got to leave the hospital doors with a baby. It was like experiencing birth and parenthood for the first time.

ONLINE RESOURCES

Academy of Breastfeeding Medicine Information on Breastfeeding for Health Care Professionals. Retrieved from https://www.bfmed.org/resources

American Academy of Pediatrics Breastfeeding Information for Families and Health Care Professionals. Retrieved from https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Breastfeeding/Pages/default.aspx

American Academy of Pediatrics. (2011). Clinical report postnatal glucose homeostasis in late-preterm and term infants. *Pediatrics, 127*(3), 575–579. doi:10.1542/peds.2010-3851

Association of Women's Health, Obstetric, Gynecologic, and Neonatal Nursing Policy Statement on Breastfeeding. Retrieved from https://www.jognn.org/article/S0884-2175(15)31769-X/abstract?utm_source=awhonn.org&utm_medium=page%2520link&utm_campaign=AWHONN_Positions&utm_content=Breastfeeding

Centers for Disease Control and Prevention. (n.d.). *Congenital heart defects information for healthcare providers*. Retrieved from https://www.cdc.gov/ncbddd/heartdefects/hcp.html

Centers for Disease Control and Prevention. (n.d.). Jaundice and kernicterus guidelines and tools for health professionals. Retrieved from http://www.cdc.gov/ncbddd/jaundice/hcp.html

La Leche League International Resources for Families and Health Care Providers Regarding Breastfeeding. Retrieved from http://www.lalecheleague.org

U.S. Department of Health and Human Services Office on Women's Health Breastfeeding Information Site for Families. Retrieved from http://www.womenshealth.gov/breastfeeding

REFERENCES

Adamkin, D. H. (2011). Clinical report-postnatal glucose homeostasis in late-preterm and term infants. *Pediatrics, 127*(3), 575–579. doi:10.1542/peds.2010-3851

Ahmed, A., & Ellsworth, P. (2012). To circ or not: A reappraisal. *Urologic Nursing, 32*(1), 10–19. doi:10.7257/1053-816X.2012.32.1.19

Alkalay, A. L., Bresee, C. J., & Simmons, C. F. (2010). Decreased neonatal jaundice readmission rate after implementing hyperbilirubinemia guidelines and universal screening for bilirubin. *Clinical Pediatrics, 49*(9), 830–833. doi:10.1177/0009922810363728

Alkalay, A. L., & Simmons, C. F. (2005). Hyperbilirubinemia guidelines in newborn infants. *Pediatrics, 115*(3), 824–825. doi:10.1542/peds.2004-2442

American Academy of Pediatrics. (2018). *Program to enhance the health & development of infants and children*. Retrieved from https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/PEHDIC/Pages/Newborn-Screening-for-CCHD.aspx

American Academy of Pediatrics Newborn Screening Authoring Committee. (2008). Screening expands: Recommendations for pediatricians and medical homes, implications for the system. *Pediatrics, 121*, 192–217. doi:10.1542/peds.2007-3021

American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. (2004). Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics, 114*, 297–316. doi:10.1542/peds.114.1.297

American Academy of Pediatrics Policy Statement. (2012). Breastfeeding and the use of human milk. *Pediatrics, 129*, e827–e841. doi:10.1542/peds.2011–3552

American Academy of Pediatrics. (2016). SIDS and other sleep related infant deaths: Updated 2016 recommendations for a safe infant sleeping environment. *Pediatrics 138*(5), 1–12.

American Academy of Pediatrics Task Force on Circumcision. (1999). Circumcision policy statement. *Pediatrics, 103*(3), 686–693. doi:10.1542/peds.103.3.686

American Speech-Language-Hearing Association. (2018). *Newborn infant hearing screening*. Retrieved from https://www.asha.org/PRPSpecificTopic.aspx?folderid=8589935234&section=Resources

Amitay, E. L., & Keinan-Boker, L. (2015). Breastfeeding and childhood leukemia incidence: A meta-analysis and systematic review. *JAMA Pediatrics, 169*(6), e151025–e151025. doi:10.1001/jamapediatrics.2015.1025

Angel, C. A. (2018). Circumcision. In T. Rosenkrantz (Ed.), Medscape. Retrieved from https://emedicine.medscape.com/article/1015820-overview

Association of Women's Health, Obstetric and Neonatal Nurses. (2011). AWHONN position statement: Newborn screening. *Journal of Obstetrics, Gynecologic & Neonatal Nursing, 40*, 136–137. doi:10.1111/j.1552-6909.2010.01213.x

Association of Women's Health, Obstetric and Neonatal Nurses. (2014). New neonatal skin care evidence-based practice guideline. *Nursing for Women's Health 17*(6), 545–546

Avila, W. M., Pordeus, I. A., Paiva, S. M., & Martins, C. C. (2015). Breast and bottle feeding as risk factors for dental caries: A systematic review and meta-analysis. *PLoS One, 10*(11), e0142922. doi:10.1371/journal.pone.0142922

Baby Friendly USA (2018, June). *Find sites*. Retrieved from https://www.babyfriendlyusa.org/find-facilities

Bartick, M., & Reinhold, A. (2010). The burden of suboptimal breastfeeding in the United States: A pediatric cost analysis. *Pediatrics, 125*(5), 1048–1056. doi:10.1542/peds.2009-1616

Bartick, M. C., Schwarz, E. B., Green, B. D., Jegier, B. J., Reinhold, A. G., Colaizy, T. T., . . . Stuebe, A. M. (2017). Suboptimal breastfeeding in the United States: Maternal and pediatric health outcomes and costs. *Maternal & Child Nutrition, 13*(1), e12366. doi:10.1111/mcn.12366

Berg, O., & Hung, K. J. (2011). Early skin-to-skin to improve breastfeeding after cesarean birth. *Journal of Obstetric, Gynecologic & Neonatal Nursing, 40*, S18–S19. doi:10.1111/j.1552-6909.2011.01242_24.x

Bhutani, V. K., Vilms, R. J., & Hamerman-Johnson, L. (2010). Universal bilirubin screening for severe neonatal hyperbilirubinemia. *Journal of Perinatology, 30*(Suppl.), S6–S15. doi:10.1038/jp.2010.98

Blackwell, J. T. (2003). Clinical practice guidelines. Management of hyperbilirubinemia in the healthy term newborn. *Journal of the American Academy of Nurse Practitioners, 15*(5), 194–198. doi:10.1111/j.1745-7599.2003.tb00358.x

Blum-Kemelor, D., & Leonberg, B. (2009). *Infant nutrition and feeding: A guide for use in the WIC and CSF programs* (FNS-288). Washington, DC: United States Department of Agriculture.

Bowatte, G., Tham, R., Allen, K. J., Tan, D. J., Lau, M. X. Z., Dai, X., & Lodge, C. J. (2015). Breastfeeding and childhood acute otitis media: A systematic review and meta-analysis. *Acta Paediatrica, 104*(S467), 85–95. doi:10.1111/apa.13151

Canadian Paediatric Society. (2007). Guidelines for detection, management and prevention of hyperbilirubinemia in term and late preterm newborn infants (35 or more weeks gestation). *Paediatrics and Child Health, 12*(5), 1B–12B. doi:10.1093/pch/12.suppl_B.1B

Carefoot, S., Williamson, P. R., & Dickson, R. (2004). The value of a pilot study in breastfeeding research. *Midwifery, 20*, 188–193. doi:10.1016/j.midw.2003.11.002

Carefoot, S., Williamson, P. R., & Dickson, R. (2005). A randomized control trial in the north of England examining the effects of skin-to-skin care on breastfeeding. *Midwifery, 21*, 71–79. doi:10.1016/j.midw.2004.09.002

Carrier, C. (2009). Back to sleep: A culture change to improve practice. *Newborn and Infant Nursing Reviews, 9*(3), 163–168. doi:10.1053/j.nainr.2009.07.006

Centers for Disease Control and Prevention. (n.d.). *Hepatitis B questions and answer for health professionals*. Retrieved from https://www.cdc.gov/hepatitis/hbv/hbvfaq.htm#D1

Centers for Disease Control and Prevention. (2016a). *What are jaundice and kernicterus*. Retrieved from https://www.cdc.gov/ncbddd/jaundice/facts.html

Centers for Disease Control and Prevention. (2016b). *Newborn screening portal*. Retrieved from https://cdc.gov/newbornscreening/

Centers for Disease Control and Prevention. (2018). *Congenital heath defects information for healthcare providers*. Retrieved from https://www.cdc.gov/ncbddd/heartdefects/hcp.html

Chen, D. C., Nommsen-Rivers, L., Dewey, K. G., & Lonnerdal, B. (1998). Stress during labor and delivery and early lactation performance. *The American Journal of Clinical Nutrition, 68*, 335–344. doi:10.1093/ajcn/68.2.335

Crenshaw, J. T. (2014). Healthy birth practice #6: Keep mother and baby together—It's best for mother, baby, and breastfeeding. *Journal of Perinatal Education, 23*(4), 211–217. doi:10.1891/1058-1243.23.4.211

Cong, X., Ludington-Hoe, S. M., Hussain, N., Cusson, R. M., Walsh, S., Vazquez, V., . . . Vittner, D. (2015). Parental oxytocin responses during skin-to-skin contact in pre-term infants. *Early Human Development, 91*(7), 401–406. doi:10.1016/j.earlhumdev.2015.04.012

Delaney, A., Meyers, A., Roger, R., Russell, F., Talavera, F., Roland, P., & Slack, C. (2012). Newborn hearing screening. Retrieved from http://emedicine.medscape.com/article/836646-overview#a1

Dennery, P. A., Seidman, D. S., & Stevenson, D. K. (2001). Neonatal hyperbilirubinemia. *New England Journal of Medicine, 344*(8), 581–590. doi:10.1056/NEJM200102223440807

Doan, T., Gardiner, A., Gay, C. L., & Lee, K. A. (2007). Breast-feeding increases sleep duration of new parents. *Journal of Perinatal and Neonatal Nursing, 21*, 200–206. doi:10.1097/01.JPN.0000285809.36398.1b

Duijts, L., Jaddoe, V. W., Hofman, A., & Moll, H. A. (2010). Prolonged and exclusive breastfeeding reduces the risk of infectious diseases in infancy. *Pediatrics, 126*(1), e18–25. doi:10.1542/peds.2008-3256

Eidelman, A. I., & Schanler, R. J. (2012). Breastfeeding and the use of human milk: Policy statement of the American Academy of Pediatrics. *Pediatrics, 129*, e827–e841. doi:10.1542/peds.2011-3552

Fort, A. & Walker, K. (2015). Improving newborn clinical outcomes with delayed bathing. Association of Women's Health, Obstetric and Neonatal Nurses Conference.

Hardcastle, T. (2010). Sucrose has been shown to have analgesic properties when administered to neonates and infants: Is there the potential for its use in post-operative pain management? *Journal of Perioperative Practice, 20*(1), 19–22. doi:10.1177/175045891002000102

Hauck, F. R., Omojokun, O. O., & Siadaty, M. S. (2005). Do pacifiers reduce the risk of sudden infant death syndrome? A meta-analysis. *Pediatrics, 116*, e715–e724. doi:10.1542/peds.2004-2631

Hauck, F. R., Thompson, J. M. D., Tanabe, K. O., Moon, R. Y., & Vennemann, M. M. (2011). Breastfeeding and reduced risk of sudden infant death syndrome: A meta-analysis. *Pediatrics, 128*, 103–110. doi:10.1542/peds.2010-3000

Hemachandra, A., Puapornpong, P., Ketsuwan, S., & Imchit, C. (2016). Effect of early skin-to-skin contact to breast milk volume and breastfeeding jaundice at 48 hours after delivery. *Journal of the Medical Association of Thailand, 99*(11), 63. Retrieved from http://www.jmatonline.com/index.php/jmat/article/view/7951

Holman, R. C., Stoll, B. J., Curns, A. T., Yorita, K. L., Steiner, C. A., & Schonberger, L. B. (2006). Necrotising enterocolitis hospitalisations among neonates in the United States. *Paediatric and Perinatal Epidemiology, 20*(6), 498–506. doi:10.1111/j.1365-3016.2006.00756.x

Horta, B. L., Loret de Mola, C., & Victora, C. G. (2015). Long-term consequences of breastfeeding on cholesterol, obesity, systolic blood pressure and type 2 diabetes: A systematic review and meta-analysis. *Acta Paediatrica, 104*(S467), 30–37. doi:10.1111/apa.13133

Horta, B. L., & Victora, C. (2013). *Short-term effects of breastfeeding: A systematic review on the benefits of breastfeeding on diarrhoea and pneumonia mortality*. Geneva, Switzerland: World Health Organization

Howard, C. R., Howard, F. M., Lanphear, B., Eberly, S., deBliek, E. A., Oakes, D., & Lawrence, R. (2003). Randomized clinical trial of pacifier use and bottle-feeding or cupfeeding and their effect on breastfeeding. *Pediatrics, 111*, 511–518. doi:10.1542/peds.111.3.511

Ibarra, B., & Goodstein, M. (2011). A parent's guide to a safe sleep environment. *Advances in Neonatal Care, 11*(1), 27–28. doi:10.1097/ANC.0b013e3182087fa5

Ip, S., Chung, M., Raman, G., Chew, P., Magula, N., DeVine, D., . . . Lau, J. (2007). *Breastfeeding and maternal and infant outcomes in developed countries* (AHRQ publication no. 07-E007). Rockville, MD: Agency for Healthcare Research and Quality.

Jensen, D., Wallace, S., & Kelsay, P. (1994). LATCH: A breastfeeding charting system and documentation tool. *Journal of Obstetric, Gynecologic, and Neonatal Nursing, 23*, 27–32. doi:10.1111/j.1552-6909.1994.tb01847.x

Johnston, C., Campbell-Yeo, M., Fernandes, A., Inglis, D., Streiner, D., & Zee, R. (2014). Skin-to-skin care for procedural pain in neonates. *Cochrane Database of Systematic Reviews*, (2), CD008435. doi:10.1002/14651858.CD008435.pub3

Kaneshiro, N. (2011). Appropriate for gestational age (AGA). *MedlinePlus*. Retrieved from http://www.nlm.nih.gov/medlineplus/ency/article/002225.htm

Keefe, M. R. (1987). Comparison of neonatal nighttime sleep-wake patterns in nursery versus rooming-in environments. *Nursing Research, 36*(3), 140–144. doi:10.1097/00006199-198705000-00002

Keefe, M. R. (1988). The impact of infant rooming-in on maternal sleep at night. *Journal of Obstetric, Gynecologic, and Neonatal Nursing, 17*(2), 122–126. doi:10.1111/j.1552-6909.1988.tb00522.x

Kernerman, E., & Newman, J. (2009). *Breastfeeding Inc.: Is my baby getting enough milk?* Retrieved from https://www.canadianbreastfeedingfoundation.org/basics/enough_milk.shtml

Khurshid, F., & Medves, J. (2017). Effectiveness of universal hyperbilirubinemia screening on newborn health: A systematic review protocol. *JBI Database of Systematic Reviews and Implementation Reports, 16*(2), 287–290. doi:10.11124/JBISRIR-2016-003338

Kleinman, R. E. (Ed.). (2008). *Pediatric nutrition handbook* (6th ed.). Elk Grove Village, IL: American Academy of Pediatrics.

Lawrence, R. A., & Lawrence, R. M. (2015). *Breastfeeding: A guide for the medical profession* (8th ed.). Maryland Heights, MO: Elsevier Mosby.

Li, D. K., Willinger, M., Petitti, D. B., Odouli, R., Liu, L., & Hoffman, H. J. (2006). Use of a dummy (pacifier) during sleep and risk of sudden infant death syndrome (SIDS): Population based case-control study. *British Medical Journal, 332*(7532), 18–22. doi:10.1136/bmj.38671.640475.55

Mabry-Hernandez, I., & Oliverio-Hoffman, R. (2010). *Ocular prophylaxis for gonococcal ophthalmia neonatorum evidence update for the U.S. Preventive Services Task Force reaffirmation recommendation statement* (AHRQ Publication No. 10–05146). Rockville, MD: Agency for Healthcare Research and Quality.

Makker, K., Alissa, R., Dudek, C., Travers, L., Smotherman, C., & Hudak, M. L. (2018). Glucose gel in infants at risk for transitional neonatal hypoglycemia. *American Journal of Perinatology, 35*(11), 1050–1056. doi:10.1055/s-0038-1639338

Moore, E. R., Bergman, N., Anderson, G. C., & Medley, N. (2016). Early skin-to-skin contact for mothers and their healthy newborn infants. *Cochrane Database of Systematic Reviews*, (11), CD003519. doi:10.1002/14651858.CD003519.pub4

National Association of Neonatal Nurses Board of Directors. (2011). Prevention of acute bilirubin encephalopathy and kernicterus in newborns: Position Statement 3049. *Advances in Neonatal Care, 11*(5S), S3–S9. doi:10.1097/ANC.0b013e31822efd64

National Newborn Screening and Genetics Resource Center. (2009). *National screening status report*. Retrieved from http://genes-r-us.uthscsa.edu/nbsdisorders.pdf

National Newborn Screening and Genetics Resource Center. (2014). *National screening status report*. Retrieved from http://genes-r-us.uthscsa.edu/nbsdisorders.pdf

Nelson, E. A. S., Yu, L., & Williams, S. (2005). International child care practices study: Breastfeeding and pacifier use. *Journal of Human Lactation, 21*, 289–295. doi:10.1177/0890334405278489

Niemelä, M., Pihakari, O., Pokka, T., & Uhari, M. (2000). Pacifier as a risk for acute otitis media: A randomized controlled trial of parental counseling. *Pediatrics, 106*, 483–488. doi:10.1542/peds.106.3.483

Okwundu, C. I., Uthman, O. A., Suresh, G., Smith, J., Wiysonge, C. S., Bhutani, V. K. (2017). Transcutaneous bilirubinometry versus total serum bilirubin measurement for newborns (Protocol). *Cochrane Database of Systematic Reviews*, (5), CD012660. doi:10.1002/14651858.CD012660

Peres, K. G., Barros, A. J. D., Peres, M. A., & Victora, C. G. (2007). Effects of breastfeeding and sucking habits on malocclusion in a birth cohort study. *Revisita De Saúde Pública (Revisit Public Health), 41*, 343–350. doi:10.1590/S0034-89102007000300004

Peres, K. G., Cascaes, A. M., Nascimento, G. G., & Victora, C. G. (2015). Effect of breastfeeding on malocclusions: A systematic review and meta-analysis. *Acta Paediatrica, 104*(S467), 54–61. doi:10.1111/apa.13103

Pérez-Escamilla, R., Martinez, J. L., & Segura-Pérez, S. (2016). Impact of the Baby-Friendly Hospital Initiative on breastfeeding and child health outcomes: A systematic review. *Maternal & Child Nutrition, 12*(3), 402–417. doi:10.1111/mcn.12294

Public Law 110–204. (2008). Newborn screening saves lives act of 2007. Retrieved from http://www.govtrack.us/congress/billtextxpd?bill=s110-1858

Quigley, M. A., Henderson, G., Anthony, M. Y., & McGuire, W. (2007). Formula milk versus donor breast milk for feeding preterm or low birth weight infants. *Cochrane Database of Systematic Review,* (4), CD002971. doi:10.1002/14651858.CD002971.pub2

Raeside, L. (2011). Physiological measures of assessing infant pain: A literature review. *British Journal of Nursing, 20*(21), 1370–1376. doi:10.12968/bjon.2011.20.21.1370

Riede, F., Wörner, C., Dähnert, I., Möckel, A., Kostelka, M., & Schneider, P. (2010). Effectiveness of neonatal pulse oximetry screening for detection of critical congenital heart disease in daily clinical routine—Results from a prospective multicenter study. *European Journal of Pediatrics, 169*(8), 975–981. doi:10.1007/s00431-010-1160-4

Ringer, S. A. (2013). Core concepts: Thermoregulation in the newborn part one: Basic mechanisms. *NeoReviews 14*(4). Retrieved from http://neoreviews.aappublications.org/content/14/4/e161

Rozance, P. J., & Hay, W. W., Jr. (2016). Modern management of preterm infants prevents adverse developmental outcomes from hypoglycemia. *Pediatrics, 138*(6), e20162881. doi:10.1542/peds.2016-2881

Stavis, R., Mawr, B. (2017). Hypothermia in neonates. *Merck Manual*. Kenilworth, N.J. USA.

Stevens, B., Yamada, J., & Ohlsson, A. (2010). Sucrose for analgesia in newborn infants undergoing painful procedures [Review]. *Cochrane Database of Systematic Reviews,* (1), CD001069. doi:10.1002/14651858.CD001069.pub3

Stokowski, L. (2011). Fundamentals of phototherapy for neonatal jaundice. *Advances in Neonatal Care, 11*(5S), 10–21. doi:10.1097/ANC.0b013e31822ee62c

Stone, S., Spencer, B., & Prater, L. (2014). Change is in the air: Facilitating skin-to-skin contact in the operating room after cesarean birth. *Nursing for Women's Health, 18*, 486–499. doi:10.1111/1751-486X.12161

Tham, R., Bowatte, G., Dharmage, S. C., Tan, D. J., Lau, M. X. Z., Dai, X., . . . Lodge, C. J. (2015). Breastfeeding and the risk of dental caries: A systematic review and meta-analysis. *Acta Paediatrica, 104*(S467), 62–84. doi:10.1111/apa.13118

Thompson, J. M., Tanabe, K., Moon, R. Y., Mitchell, E. A., McGarvey, C., Tappin, D., . . . Hauck, F. R. (2017). Duration of breastfeeding and risk of SIDS: An individual participant data meta-analysis. *Pediatrics, 140*(5), e20171324. doi:10.1542/peds.2017-1324

Ullah, S., Rahman, K., & Hedayati, M. (2016). Hyperbilirubinemia in neonates: Types, causes, clinical examinations, preventive measures and treatments: A Narrative review article. *Iranian Journal of Public Health, 45*(5), 558–568.

Vennemann, M. M., Bajanowski, T., Brinkmann, B., Jorch, G., Yücesan, K., Sauerland, C., & Mitchell, E. A. (2009). Does breastfeeding reduce the risk of sudden infant death syndrome? *Pediatrics, 123*(3), e406–e410. doi:10.1542/peds.2008-2145

Vogel, A. M., Hutchison, B. L., & Mitchell, E. A. (2001). The impact of pacifier use on breastfeeding: A prospective cohort study. *Journal of Paediatrics and Child Health, 37*, 58–63. doi:10.1046/j.1440-1754.2001.00581.x

Waldenström, U., & Swenson, A. (1991). Rooming-in at night in the postpartum ward. *Midwifery, 7*(2), 82–89. doi:10.1016/S0266-6138(05)80232-3

Walker, M. (1993). A fresh look at the risks of artificial infant feeding. *Journal of Human Lactation, 9*(2), 97–107. doi:10.1177/089033449300900222

Wambach, K., & Riordan, J. (Eds.). (2016). *Breastfeeding and human lactation* (5th ed.). Sudbury, MA: Jones & Bartlett.

Wight, N., & Marinelli, K. A. (2014). ABM Clinical Protocol #1: Guidelines for Blood Glucose Monitoring and Treatment of Hypoglycemia in Term and Late-Preterm Neonates, Revised 2014. *Breastfeeding Medicine, 9*(4), 173–179. http://doi.org/10.1089/bfm.2014.9986

World Health Organization. (2007). *Safe preparation, storage, and handling of powdered infant formula guidelines*. Geneva, Switzerland: World Health Organization (Joint publication with the Food and Agriculture Organization of the United Nations).

World Health Organization. (2018). Ten steps to successful breastfeeding (revised 2018). Retrieved from http://www.who.int/nutrition/bfhi/ten-steps/en

Unit III: Systems Assessment and Management of Disorders

CHAPTER 6

Respiratory System

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INTRODUCTION

The mechanisms that bring about normal pulmonary function are complex. The clinician must fully comprehend the physiologic processes associated with neonatal respiratory diseases. Only through advanced knowledge can the clinician efficiently assess and evaluate the newborn's respiratory status. Systematic use of these assessment skills allows the clinician, as part of the collaborative team, to positively affect patient outcome.

EMBRYOLOGIC DEVELOPMENT OF THE LUNG

Pulmonary development of the embryo proceeds along a predetermined sequence throughout gestation (Greenough & Milner, 2005). Pulmonary development begins with the formation of an outpouching of the embryonic foregut during the fourth week of gestation. Sequential branching of the lung bud, which appears at about 4 weeks and is complete by the sixth week, marks the embryonic phase of lung development. Weeks 7 to 16, the pseudoglandular phase, are marked by the formation of conducting airways by branching of the aforementioned lung buds. This phase ends with completion of the conducting airways. The canalicular phase follows through week 28, when gas exchange units, known as acini, develop. Surfactant-producing type II pneumocytes begin to form during the latter part of this phase. Mature, vascularized gas exchange sites form during the saccular phase, which spans the 29th through 35th weeks. During this phase, the interstitial space between alveoli thins, so respiratory epithelial cells tightly contact developing capillaries. The alveolar development phase, marked by expansion of the gas exchange surface area, begins at 36 weeks and extends into the postnatal period. Additional alveoli continue to develop well into childhood, perhaps as late as the seventh year of life (Table 6.1). The alveolar wall and interstitial spaces become very thin, and the single capillary network comes in close proximity to the alveolar membrane. No firm boundaries separate the phases of lung development, and gas exchange, albeit inefficient, is possible relatively early in gestation, even before mature, vascularized gas exchange sites form. Lung development is a continuum that is marked by rapid structural changes. Interference at any time by premature birth or by disease introduces the possibility of inducing lung injury.

TABLE 6.1

STAGES OF NORMAL LUNG GROWTH

Phase	Timing	Major Event
Embryonic	Weeks 4–6	Formation of proximal airway
Pseudoglandular	Weeks 7–16	Formation of conducting airways
Canalicular	Weeks 17–28	Formation of acini
Saccular	Weeks 29–35	Development of gas exchange sites
Alveolar	Weeks 36 through postnatal life	Expansion of surface area

NEWBORN PULMONARY PHYSIOLOGY AND THE ONSET OF BREATHING

The fetal lung is fluid filled, underperfused, and dormant with regard to gas exchange. The fetal lung receives only approximately 10% of the cardiac output (CO). Because the placenta is the gas exchange organ in fetal life, high blood flow is preferentially directed toward it rather than to the lungs. The pulmonary vasculature maintains a high vascular resistance. Consequently, most of the right ventricular output is shunted from the pulmonary artery across the ductus arteriosus into the aorta, bypassing the pulmonary circulation.

Within moments after the umbilical cord is clamped, the newborn undergoes a transformation from a fetus floating in amniotic fluid to an air-breathing neonate. When normal breathing occurs after birth, the ensuing chain of events converts the fetal circulation to the adult pattern of circulation. Lung fluid is absorbed and replaced with air, thus establishing lung volume and allowing for normal neonatal pulmonary function. The process of fetal lung fluid absorption begins before birth when the rate of alveolar fluid secretion

declines. Reabsorption speeds up during labor. Animal data suggest that as much as two-thirds of the total clearance of lung fluid occurs during labor due to the cessation of active chloride secretion into the alveolar space. Perinatal fluid clearance is also related to epithelial sodium channels (ENaC) induced by the increase in serum cortisol after delivery (Janér, Pitkänen, Helve, & Andersson, 2011). Oncotic pressure favors the movement of water from the air space back into the interstitium and into the vascular space. With the onset of breathing and lung expansion, water moves rapidly from the air spaces into the interstitium and is removed from the lung by lymphatic and pulmonary blood vessels. Since a large proportion of the clearance of lung fluid occurs during the labor process, neonates born without labor after a scheduled cesarean section are at particularly high risk for delayed absorption of fetal lung fluid and thus for transient tachypnea of the newborn (TTN). Late preterm infants whose mothers received betamethasone have lower rates of TTN presumably due to the influence of corticosteroids on upregulation of ENaC channels (Gyamfi-Bannerman et al., 2016). Birth prior to 38 weeks by elective scheduled cesarean section is especially associated with an increased risk of respiratory disorders and an increase in mortality risk (Tita et al., 2009).

Several cardiac changes must take place to complete the process of transition from the intrauterine to extrauterine environment. With the onset of breathing, highly negative intrathoracic pressures are generated with inspiratory efforts, filling the alveoli with air. Replacing alveolar fluid with air causes a precipitous decrease in hydrostatic pressure in the lung, leading to a decrease in pulmonary artery pressure. The resultant decrease in right atrial pressure and increase in pulmonary blood flow leads to an increase in alveolar oxygen tension (Pa_{O_2}) which causes constriction of the ductus arteriosus, which normally shunts right ventricular blood away from the lungs. Clamping of the umbilical cord removes the large, low-resistance, placental surface area from the circulation. This change in resistance causes an abrupt increase in systemic arterial pressure, reflected all the way back to the left atrium. As left atrial pressure rises, the flap valve opening between the atria, known as the foramen ovale, is pushed shut. This closure prevents blood from bypassing the lungs by eliminating the shunt across the foramen ovale from the right atrium to the left atrium. These simultaneous changes wherein the systemic vasculature resistance exceeds that of the pulmonary vasculature allow physiologic closure of both the foramen ovale and ductus arteriosus. The infant successfully converts from the pattern of fetal circulation to neonatal circulation when blood coming from the right ventricle flows in its new path of least resistance (lower pressure) to the lungs, instead of shunting across the foramen ovale to the left atrium or across the ductus arteriosus from the pulmonary artery to the aorta.

Understanding normal breathing and ventilation enables the clinician to assess the infant in respiratory distress and devise strategies for management. The respiratory system is composed of the following: (a) the pumping system (the chest wall muscles, diaphragm, and accessory muscles of respiration), which moves free gas into the lungs; (b) the bony rib cage, which provides structural support for the respiratory muscles and limits lung deflation; (c) the conducting airways, which connect gas-exchanging units with the outside but offer resistance to gas flow; (d) an elastic element, which offers some resistance to gas flow but provides pumping force for moving stale gas out of the system; (e) air–liquid interfaces, which generate surface tension that opposes lung expansion on inspiration but supports lung deflation on expiration; and (f) the abdominal muscles, which aid exhalation by active contraction.

Limitations in the respiratory system predispose the newborn to respiratory difficulty. The circular, poorly ossified rib cage, with a flat instead of angular insertion of the diaphragm, is less efficient at generating negative intrathoracic pressure during inhalation. The highly compliant chest wall often moves in a contrary manner to the desired flow of air. Small muscles and a relative paucity of type I muscle fibers hinder the strength and endurance of respiratory muscles. The newborn has a relatively low functional residual capacity (lung volume at the end of exhalation) because the comparatively floppy chest wall offers little resistance to collapse, even when a normal amount of functional surfactant is present.

Surface tension is the force that arises from the interaction among the molecules of a liquid. Molecules in the interior of the liquid bulk are attracted to each other, but molecules on the surface of the liquid are attracted to other molecules in the interior of the liquid, which results in the movement of the surface molecule toward the bulk of the liquid. This explains why a droplet of water over a surface tends to adopt a given size and not continuously expand. If we think of the alveolus as a soap bubble, the molecules of the wall of the bubble are attracted to each other, which tend to collapse the bubble. The higher the surface tension, the faster the bubble collapses. The pressures across the wall of the bubble act against the surface tension and avoid the collapse of the bubble. The relationship between the surface tension and the distending pressures and the pressure across the wall of the bubble are described by Laplace's law, as shown in the following equation:

$$P = \frac{2ST}{r}$$

where P is pressure, ST is surface tension, and r is radius of the alveolus. It is difficult to inflate a small or collapsed alveolus because it has a very small diameter. As its volume increases, the pressure needed to continue inflation becomes progressively less—that is, compliance of the alveolus and thus compliance of the lung have improved. Coating the alveoli with an agent that decreases surface tension reduces the effort required to inflate the lungs from a low volume.

An alveolar cell known as the type II pneumocyte produces pulmonary surfactant. Surfactant is a mixture of proteins and phospholipids that naturally coats the mature alveoli, preventing alveolar collapse and loss of lung volume during expiration—that is, as expiration ensues and the lung deflates, the alveolar diameter becomes smaller. Surfactant coating of the alveolus reduces surface tension so that collapse is prevented and less pressure is required to reinflate it with the next inspiration. Neonates with respiratory distress syndrome (RDS) have surfactant deficiency. In the absence of surfactant, surface tension is high, and the tendency is toward collapse of alveoli at end expiration and resulting microatelectasis.

Compliance is the elasticity, or distensibility, of the lung. It is expressed as the change in volume caused by a change in pressure as follows:

$$CL = \frac{V}{P}$$

where CL is compliance of the lung, V is volume, and P is pressure. The higher the compliance, the larger the volume delivered to the alveoli per unit of applied inspiratory pressure. Surface tension and compliance are particularly important in the preterm infant with RDS. Surface tension is a force that opposes lung expansion. Surfactant deficiency leads to increased surface tension in the alveoli. Lungs with higher surface tension are more difficult to inflate. During expiration, some alveoli collapse. This results in a decreased lung volume at the end of expiration (low functional residual capacity). Clinically, the presence of retractions and other signs of respiratory distress such as nasal flaring and grunting manifest the effects of this increased surface tension. Respiratory muscles contract to inflate the lungs against the surface tension that acts in the opposite direction. The negative pleural pressure easily deforms

the floppy thoracic wall of the preterm infant. When a preterm infant with RDS is intubated, a high peak inspiratory pressure (PIP) is required to expand the thorax (i.e., tidal volume is obtained only with a high change in pressure). After surfactant is administered, chest expansion increases with the same PIP. This effect (increased compliance) is due to a decrease in surface tension (i.e., a smaller force opposing lung distention). Thus the tidal volume obtained with the same PIP is increased. Before surfactant is administered, it is very difficult to inflate the lung because compliance is low. After surfactant is administered, surface tension decreases, and it becomes easier to inflate the lung (i.e., compliance is improved).

Resistance is a term used to describe the characteristics of gas flow through the airways and pulmonary tissues. Resistance can be thought of as the capacity of the lung to resist airflow. The principal component of resistance is determined by the small airways. Pressure is required to force gas through the airways (airway resistance) and to overcome the forces of the lung and chest wall, which work to deflate the respiratory system (tissue resistance). At a specific flow rate, resistance is described by the following equation:

$$R = \frac{P1 - P2}{V}$$

where $P1$ and $P2$ are pressures at opposite ends of the airway, and V is the flow rate of gas (volume per unit of time). Resistance increases as airway diameter decreases. Because the infant has airways of relatively small radius, the resistance to gas flow through those airways is high. Poiseuille's law recognizes that resistance to flow through a cylindrical object is inversely proportional to the fourth power of the radius.

$$R = \frac{8\eta L}{2\pi r^4}$$

In other words, if the radius of the airway is decreased by half, the resulting resistance to flow through the airway is increased 16-fold.

The time constant is the time necessary for airway pressure to partially equilibrate throughout the respiratory system and equals the mathematic product of compliance and resistance. In other words, the time constant is a measure of how quickly the lungs can inhale or exhale. It takes approximately five time constants to complete inhalation and exhalation. The time constant (K_t) is directly related to both compliance (C) and resistance (R). This relationship is described by the following equation:

$$K_t = C \times R$$

An infant with RDS has decreased compliance, so the time constant of the respiratory system is relatively short. In such an infant, little time is required for pressure to equilibrate between the proximal airway and alveoli, so short inspiratory and expiratory times may be appropriate during mechanical ventilation. This allows the child with RDS to be ventilated with higher rates than would commonly be tolerated in most other populations. When compliance improves (increases), however, the time constant becomes longer. If sufficient time is not allowed for expiration, the alveoli may become overdistended due to gas trapping, and an air leak may result.

Blood Gas Analysis and Acid–Base Balance

Oxygen diffuses across the alveolar-capillary membrane, moved by the difference in oxygen pressure between the alveoli and the blood. In the blood, oxygen dissolves in the plasma and binds to hemoglobin. Thus, arterial oxygen content (Cao_2) is the sum of dissolved and hemoglobin-bound oxygen, as is shown by the following equation:

$$Cao_2 = (1.37 \times Hb \times Sao_2)\ (0.003 \times Pao_2)$$

where Cao_2 is arterial oxygen content (mL/100 mL of blood), 1.37 is the milliliters of oxygen bound to 1 g of hemoglobin at 100% saturation, Hb is hemoglobin concentration per 100 mL of blood (g/100 mL), Sao_2 is the percentage of hemoglobin bound to oxygen (%), 0.003 is the solubility factor of oxygen in plasma (mL/mmHg), and Pao_2 is oxygen partial pressure in arterial blood (mmHg).

In the equation for arterial oxygen content, the first term—$(1.37 \times Hb \times Sao_2)$—is the amount of oxygen bound to hemoglobin. The second term—$(0.003 \times Pao_2)$—is the amount of oxygen dissolved in plasma. Most of the oxygen in the blood is carried by hemoglobin. For example, if a premature infant has a Pao_2 of 60 mmHg, an Sao_2 of 92%, and a hemoglobin concentration of 14 g/100 mL, then Cao_2 is the sum of oxygen bound to hemoglobin $(1.37 \times 14 \times 0.92) = 17.6$ mL, plus the oxygen dissolved in plasma $(0.003 \times 60) = 0.1$ mL. In this typical example, only less than 1% of oxygen in blood is dissolved in plasma; more than 99% is carried by hemoglobin. If the infant has a sudden decrease in the hemoglobin concentration to 10.5 g/dL but Pao_2 and Sao_2 remain the same, then Cao_2 $(1.37 \times 10.5 \times 0.92) + (0.003 \times 60)$ equals 13.4 mL/100 mL of blood. Thus, without any change in Pao_2 or Sao_2, a 25% decrease in hemoglobin concentration (from 14 to 10.5 g/dL) reduces the amount of oxygen in arterial blood by 24% (from 17.6 to 13.4 mL/100 mL of blood). This is an important concept for clinicians who care for patients with respiratory disease. Sao_2 and hemoglobin should be monitored and, if low, corrected to maintain adequate tissue oxygenation. Besides Sao_2 and hemoglobin, CO is the other major determination of oxygen delivery to the tissues.

The force that loads hemoglobin with oxygen in the lungs and unloads it in the tissues is the difference in partial pressure of oxygen. In the lungs, alveolar oxygen partial pressure is higher than capillary oxygen partial pressure, so that oxygen moves to the capillaries and binds to the hemoglobin. Tissue partial pressure of oxygen is lower than that of the blood, so oxygen moves from hemoglobin to the tissues. The relationship between partial pressure of oxygen and hemoglobin is better understood with the oxyhemoglobin dissociation curve (Figure 6.1). Several factors can affect the affinity of hemoglobin for oxygen. Alkalosis, hypothermia, hypocapnia, and decreased levels of 2,3-diphosphoglycerate (2,3-DPG) increase the affinity of hemoglobin for oxygen (as shown in Figure 6.1 by a left shift of the curve). Acidosis,

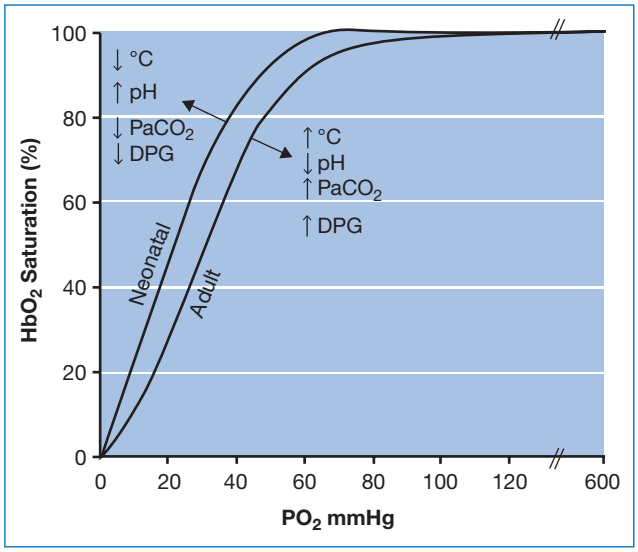

FIGURE 6.1 Oxyhemoglobin equilibrium curves of blood from term infants at birth and from adults (at pH 7.40).

hyperthermia, hypercapnia, and increased 2,3-DPG have the opposite effect, decreasing the affinity of hemoglobin for oxygen, so that the hemoglobin dissociation curve shifts to the right. This characteristic of hemoglobin facilitates oxygen loading in the lung and unloading in the tissue, where the pH is lower and alveolar carbon dioxide tension ($Paco_2$) is higher. Fetal hemoglobin, which has a higher affinity for oxygen than adult hemoglobin, is more fully oxygen-saturated at lower Pao_2 values. This is represented by a leftward shift on the hemoglobin oxygen dissociation curve.

Once loaded with oxygen, the blood should reach the tissues to transfer oxygen to the cells. Oxygen delivery to the tissue depends on CO and Cao_2, as described in the following equation:

$$\text{Oxygen Delivery} = CO \times Cao_2$$

In the case of the infant discussed previously, increased CO compensates for the decrease in Cao_2 that results from anemia. The key concept is that when a patient's oxygenation is assessed, more information than just Pao_2 and Sao_2 should be considered. Pao_2 and Sao_2 may be normal, but, if hemoglobin concentration is low or CO is decreased, oxygen delivery to the tissues is decreased. With this approach, the clinician should be able to better plan the interventions needed to improve oxygenation.

As in the adult, the acid–base balance in the neonate is maintained within narrow limits by complex interactions between the pulmonary system (which eliminates carbon dioxide) and the kidneys (which conserve carbon dioxide and eliminate metabolic acids). Carbon dioxide elimination, which is more efficient than oxygenation across the alveolar-capillary membrane, is usually not as problematic as oxygenation. Carbon dioxide has a high solubility coefficient, so cellular diffusion is efficient and no measurable partial pressure gradient exists between venous blood and the tissues. Therefore, elevated carbon dioxide tension (Pco_2) values in arterial blood samples nearly always indicate ventilatory dysfunction. Dissolved carbon dioxide moves rapidly across cell membranes of peripheral chemoreceptors, thereby making them sensitive to changes in ventilation. Increased intracellular Pco_2 elevates the cellular hydrogen ion concentration as carbon dioxide combines with water to form carbonic acid. This stimulates neural impulses to the medulla, which in turn stimulates respiration. However, excessively high Pco_2 levels and acidosis can depress ventilation. Acid–base balance is controlled by homeostatic mechanisms and is expressed by the Henderson–Hasselbalch equilibrium equation:

$$pH = 6.1 + \frac{\log HCO_3^-}{0.03 \times Pco_2}$$

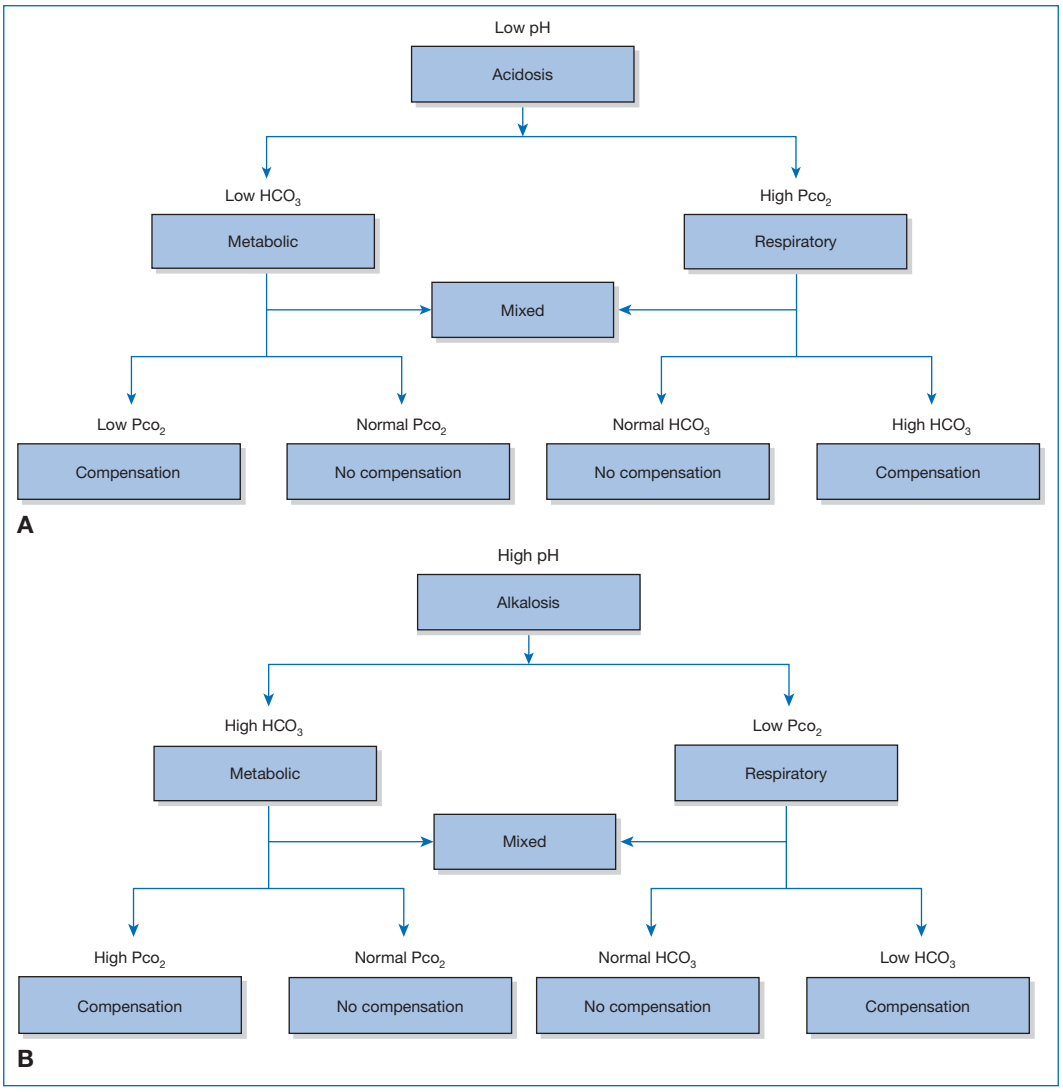

FIGURE 6.2 Acid–base balance: diagnostic approach. (A) Low pH. (B) High pH.

It can be seen from this mathematical relationship that acid–base balance depends on the interplay of bicarbonate ion (HCO_3^-) and carbon dioxide (CO_2). Low pH (in other words, acidosis) can contribute to vasoconstriction and can result in worsening hypoxemia caused by extrapulmonary shunt across the ductus or foramen ovale. A pH of 7.20 or higher is generally considered safe in preterm infants with RDS (SUPPORT Study Group et al., 2010). A pH of less than 7.0 is not well tolerated and is associated with a poor survival rate in these patients.

If $Paco_2$ rises above normal, as in hypoventilation, pH declines and the patient suffers from respiratory acidosis. The patient with a chronic respiratory acidosis may retain bicarbonate, thus self-inducing a compensatory metabolic alkalosis. A patient who is hyperventilated with a low $Paco_2$ has respiratory alkalosis. Depressed bicarbonate ion concentration (less than approximately 20 mmol/L in plasma) is called metabolic acidosis and can be associated with any cause of anaerobic metabolism, such as poor CO from congenital heart disease—for example, hypoplastic left heart syndrome or severe aortic coarctation—or from myocardial ischemia, myocardiopathy, myocarditis, hypoxia, necrotizing enterocolitis, or septic shock. Metabolic acidosis that results from renal bicarbonate wasting commonly develops in extremely premature infants. Less common causes for prolonged and severe metabolic acidosis are the inborn errors of metabolism, including urea cycle defects and aminoacidopathies.

The clinician should become proficient at interpreting blood gas data. With knowledge of the accepted normal values and definitions of the simple blood gas disorders and their compensatory mechanisms, the clinician can examine data in light of the disease process and interpret blood gas values in a fairly straightforward manner. Normally, the body does not overcompensate for a pH above or below the normal range. Therefore, when presented with an abnormal pH, the clinician should rapidly determine whether acidosis (Figure 6.2A) or alkalosis (Figure 6.2B) exists. An examination of $Paco_2$ and HCO_3^- determines whether the process is respiratory, metabolic, or mixed. The clinician should determine which derangement occurred first. For example, an acidotic, acutely ill hypoxemic infant with a high $Paco_2$ and depressed HCO_3^- is usually hypoventilating and suffering metabolic acidosis secondary to anaerobic metabolism. The infant with a low $Paco_2$ is hyperventilating, either spontaneously or secondary to overzealous mechanical ventilation. A concomitantly low pH and low $Paco_2$ indicate that the infant is compensating for metabolic acidosis with hyperventilation in an effort to normalize the pH. A pure metabolic alkalosis with high pH can be caused by bicarbonate administration, loop diuretics such as furosemide, or gastric losses due to pyloric stenosis or gastric suctioning. Infants with bronchopulmonary dysplasia (BPD) usually have a compensated respiratory acidosis, with an elevated $Paco_2$ and concomitantly elevated HCO_3^-. The pH may be in the normal range or slightly acidotic. A severely depressed pH usually indicates acute decompensation.

ASSESSMENT OF THE NEONATE WITH RESPIRATORY DISTRESS

The assessment of a neonate with respiratory distress should always begin with the compilation of a detailed perinatal history. In some cases, the history is difficult to obtain, especially when the infant has been transferred from one center to another, often with incomplete records. Even so, every effort should be made to obtain as much pertinent information as possible. The clinician is often able to gain important supplemental information from the father or visiting relatives at the bedside. A review of the maternal–perinatal history and a complete physical examination, combined with a limited laboratory and radiologic evaluation, leads to a timely diagnosis in most circumstances. Many neonatal diseases, including many with nonpulmonary origins, may manifest with signs of respiratory distress. Therefore, a comprehensive differential diagnosis must be considered (Figure 6.3).

History

In most situations, data from a patient's history can direct the clinician to the correct diagnosis of neonatal respiratory distress. The prenatal record should be reviewed carefully for possible causes of the infant's difficulties. The mother's age, gravidity, parity, blood

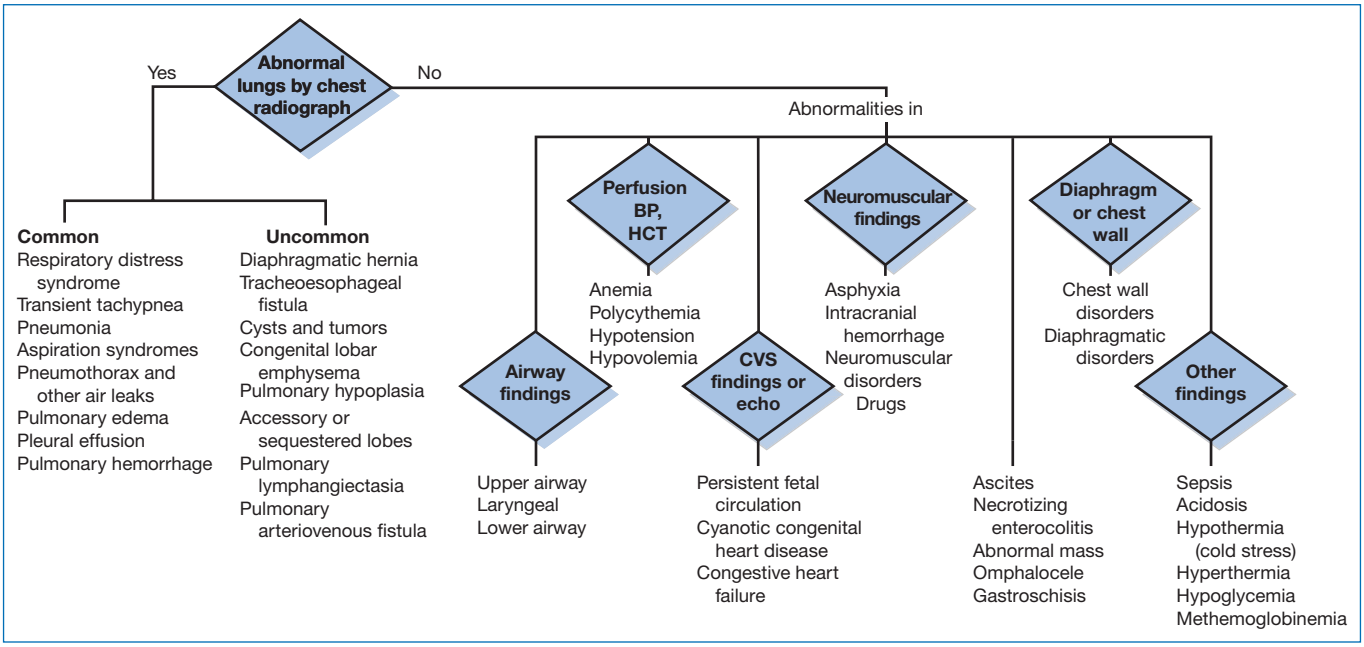

FIGURE 6.3 Diagnostic algorithm for the neonate with acute respiratory distress.

BP, blood pressure; HCT, hematocrit.

type, and Rh status should be recorded. The obstetrician's best estimate of gestational age should be documented as determined by first-trimester ultrasound or last menstrual period. Ultrasonography often provides information related to anomalies and amniotic fluid volume, which is useful in the anticipation of required support at birth. Historical information such as previous preterm birth is relevant, as it is often associated with an increased risk of premature delivery in subsequent pregnancies. Because excessive maternal weight gain occurs with diabetes, multiple gestation, or polyhydramnios, prepregnancy weight and total gain should be noted. The clinician is often alerted to the possibility of gestational diabetes with abnormal glucose tolerance screening results, which again should be reflected in the prenatal record.

The duration of membrane rupture or oligohydramnios, the presence of maternal fever with or without accompanying chorioamnionitis, and the presence of meconium-stained amniotic fluid are important pieces of information that may help in the differential diagnosis of a newborn with respiratory distress. Additionally, antepartum and intrapartum administration of certain medications may affect respiratory outcomes. **Quality and Safety: Administration of steroids to the mother reduces the likelihood that RDS will develop in the infant; administration of narcotics to the mother close to delivery may result in poor respiratory effort by an otherwise normal infant.** The use of magnesium sulfate for either neuroprotection or for tocolysis does not result in cardiorespiratory depression or need for increased resuscitation (De Jesus et al., 2015; Johnson et al., 2012).

Physical Examination of the Respiratory System

One or more of the major signs of respiratory difficulty (e.g., cyanosis, tachypnea, grunting, retractions, and nasal flaring) are usually present in neonates with both pulmonary and nonpulmonary causes of respiratory distress. Observation of the distressed infant with the unaided eye and ear is the clinician's first step in the physical assessment. Cyanosis may be central, as caused by pulmonary disease and cyanotic heart disease, or peripheral, as occurs in conditions with impaired CO. However, pulse oximetry more accurately detects hypoxemia as considerable interobserver variability has been reported in clinical detection of cyanosis (O'Donnell et al., 2007). Acrocyanosis, or cyanosis noted in the extremities, is a common normal finding in newborns during the first few days after birth. Tachypnea typically manifests in infants with decreased lung compliance, such as RDS, whereas patients with high airway resistance (e.g., airway obstruction) usually have deep but slow breathing. Grunting is produced by an adduction of vocal cords during expiration. Grunting holds gas in the lungs throughout expiration, which helps maintain lung volume and avoid alveolar collapse. At the end of expiration, the gas is released and rapidly propelled, causing an audible grunt. Grunting is more typical of infants with decreased functional residual capacity, such as preterm infants with RDS. Chest wall retractions occur more often in very premature infants because of the highly compliant chest wall (Carlo & Di Fiore, 2011). When the infant is intubated, observation of the chest gives important information. Careful observation of chest wall excursions produced by the ventilator allows the clinician to adjust the magnitude of the ventilator pressure so that optimal gas exchange is achieved while risk of volutrauma is minimized. The chest of an intubated infant should move the same or only slightly less than that of a healthy spontaneously breathing infant. The clinician should assess the appropriateness of the magnitude of the chest expansion in ventilated patients. **Emergency Alert: A reported abrupt decrease in the chest rise may indicate atelectasis, a plugged endotracheal tube, a pneumothorax, a leak in the circuit, or ventilator failure. Slow decreases in the chest rise over hours may indicate a deteriorating lung compliance or gas trapping. An overinflated thorax, as determined from radiographs, is a sign of gas trapping. In the intubated infant, this observation should prompt the clinician to decrease the positive end-expiratory pressure (PEEP) or expiratory time so that gas trapping and air leakage are prevented. An anguished intubated infant with cyanosis and gasping efforts may have endotracheal tube obstruction.**

Careful attention should be given to the sounds that emanate from the respiratory tract, as variations in quality often aid in localization of the source of respiratory distress. Stridor is common in neonates with upper airway and laryngeal lesions. Inspiratory stridor occurs most often with upper airway and laryngeal lesions, whereas expiratory stridor suggests lower airway problems. Hoarseness is a common sign of laryngeal disorders. Forced inspiratory efforts may indicate upper airway or laryngeal involvement, whereas expiratory wheezes suggest a lower airway disease. Congenital airway disorders that may cause respiratory distress in the neonate are included in Figure 6.3.

Auscultation of the chest further aids the examiner. Because infants with RDS have low lung volumes, breath sounds are faint, usually without rales. In comparison, the infant with pneumonia may have rales indicative of alveolar filling. Auscultation allows the clinician to detect the presence of secretions in the airway and to evaluate the response to physiotherapy and suctioning. Rhonchi may be heard in neonates with airway disease, such as meconium aspiration syndrome (MAS). **Emergency Alert: Unequal breath sounds may be due to a pneumothorax or to one of the many causes of diminished ventilation to a lung lobe (e.g., atelectasis, mainstem bronchial intubation, and pleural effusion). A shift of the apex of the heart can occur with a pneumothorax, diaphragmatic hernia, unilateral pulmonary interstitial emphysema, pleural effusion, dextrocardia, or atelectasis, which may be differentiated by transillumination of the chest and chest imaging. Dullness to percussion may be due to a pleural effusion or solid mass. Muffled heart tones suggest a pneumopericardium or a pericardial effusion.** Respiratory distress may occur in many chest wall disorders that restrict rib cage movements. Increased oral secretions and choking with feedings are common in neonates with a tracheoesophageal fistula. Because newborns are obligate nasal breathers, those with choanal atresia typically improve with crying and have worsening respiratory distress at rest or with feeding. Characteristic Potter facies, bell-shaped chest, and other compression deformities and contractures may be present in neonates with hypoplastic lungs secondary to oligohydramnios.

Examination of the cardiovascular system and assessment of peripheral perfusion yield many clues toward a diagnosis. Pallor and poor perfusion may indicate anemia, hypotension, or hypovolemia. Polycythemia with plethora may also cause respiratory distress. Cardiovascular signs of congestive failure (e.g., hyperactive precordium, tachycardia, and hepatomegaly), poor CO, pathologic murmurs, decreased femoral pulses, and non-sinus rhythm suggest a primary cardiac cause for the respiratory distress.

When hypotonia, muscle weakness, or areflexia accompanies respiratory distress, a neuromuscular cause should be considered (Box 6.1). In such cases, an accompanying history of less frequent fetal movement and polyhydramnios is often present. Sometimes a history of muscular disease exists in the family. Brachial plexus injury or fracture of a clavicle may accompany phrenic nerve injury and diaphragm paralysis.

Abnormalities found on abdominal examination enlighten the examiner to other causes of respiratory difficulty. Abdominal distention that results from causes such as ascites, necrotizing

Box 6.1

NEUROMUSCULAR DISORDERS THAT MAY CAUSE RESPIRATORY DISTRESS IN THE NEONATE

- Myopathies
- Myasthenia gravis
- Werdnig–Hoffmann (spinal muscular atrophy)
- Spinal cord disorder
- Poliomyelitis
- Others

Source: Adapted from Battista, M. A., & Carlo, W. A. (1992). Differential diagnosis of acute respiratory distress in the neonate. *Tufts University School of Medicine and Floating Hospital for Children Reports on Neonatal Respiratory Diseases, 2*(3), 1–4, 9–11.

Box 6.2

CAUSES OF LATE RESPIRATORY DISTRESS IN THE NEONATE

- BPD
- Pneumonia (bacterial, viral, or fungal)
- Congestive heart failure
- Recurrent pneumonitis or aspiration
- Upper airway obstruction
- Wilson–Mikity syndrome
- Idiopathic pulmonary fibrosis (Hamman–Rich syndrome)
- Pulmonary lymphangiectasia
- Cystic fibrosis
- Immature lungs

BPD, broncho-pulmonary dysplasia.

enterocolitis, abdominal mass, ileus, or tracheoesophageal fistula can cause respiratory distress, whereas a scaphoid configuration of the abdomen suggests a diaphragmatic hernia.

Other nonpulmonary disorders such as sepsis, metabolic acidosis, hypothermia, hyperthermia, hypoglycemia, and methemoglobinemia may also cause respiratory distress in the neonate.

Radiographic and Laboratory Investigation. Radiographic examination is often the most useful part of the laboratory evaluation and may serve to narrow the differential diagnosis. An anteroposterior view is usually sufficient, but a lateral chest radiograph may be useful when fluid, masses, or pneumothorax is suspected. Other diagnostic imaging techniques (ultrasonography, fluoroscopy, computed tomography, or magnetic resonance imaging) may be helpful in selected patients. Bronchoscopy allows direct visualization of the upper airway. This technique, albeit invasive and technically difficult, may in selected cases be a great aid in the differential diagnosis and treatment of patients with a suspected airway lesion.

Much can be learned from a relatively small battery of laboratory tests. In the neonatal intensive care unit (NICU) setting, the clinician is often required to collect specimens for and interpret the results of physiologic testing. Considerable skill is required in sampling both venous and arterial blood from small patients who are at substantial risk for iatrogenic anemia and vascular damage. Ideally, the hospital laboratory is equipped to do most routine tests on microliter quantities of blood. The clinician must monitor total quantities of blood sampled from the infant and be alert to the development of iatrogenic anemia.

Analysis of arterial blood for pH and gas tensions is perhaps one of the most common tasks of the clinicians caring for the infant with respiratory illness. Noninvasive methods to assess gas exchange, such as transcutaneous blood gas measurements or oxygen saturation, are very useful. Because oxygen delivery to the tissues so intimately depends on circulating red blood cell volume, a hematocrit should be performed.

COMMON DISORDERS OF THE RESPIRATORY SYSTEM

A large variety of respiratory disorders occur in neonates, the most common of which are discussed here. Figure 6.3 lists both pulmonary and nonpulmonary disorders that cause respiratory symptoms in the newborn infant. Several diseases have their roots in the neonatal period and extend into infancy (Box 6.2). The most common is BPD, a chronic lung disease that affects newborns, mainly premature infants exposed to mechanical ventilation for RDS or other respiratory problems.

Respiratory Distress Syndrome

RDS, formerly known as hyaline membrane disease (the term *hyaline membrane disease* originated from the histological observation of alveolar space lined by an eosinophilic membrane formed by cellular debris), is the most common cause of respiratory distress in premature neonates (Hamvas, 2011). RDS is common in preterm infants. Most children born extremely premature have RDS, and the incidence increases as gestational age decreases. The incidence decreases from 98% at 23 weeks to 86% at 28 weeks. Approximately 97% of 23 week infants are treated with surfactant. This decreases to 65% at 28 weeks (Stoll et al., 2010). In rare cases, RDS develops in full-term infants born to mothers with diabetes or in full-term infants with perinatal asphyxia.

Antenatal Steroids. Acceleration of lung maturation with antenatal steroids is now the standard of care in women with preterm labor of up to 34 weeks. Antenatal corticosteroid therapy to the mothers of preterm fetuses of up to 34 weeks significantly reduces the incidence of RDS with odds ratios of around 0.5 and decreases mortality, with odds ratios of around 0.6 (Roberts, Brown, Medley, & Dalziel, 2017). Subgroup analyses confirm that these benefits occur regardless of race and gender. No adverse effects have been reported with the usual single course of antenatal steroids. There are also other nonrespiratory benefits of steroid administration to mothers, including reductions in intraventricular hemorrhage and necrotizing enterocolitis. The current guidelines recommend giving steroids to mothers between 23 and 34 weeks' gestation; however, emerging data at the limits of viability show benefits to giving steroids to infants as early as 22 weeks' gestation with a lower mortality at every gestational age between 23 and 27 weeks' gestation (Carlo et al., 2011). Improved survival is additionally seen when infants only receive a partial steroid course (Carlo et al., 2011; Travers et al., 2018).

Treatment. The lungs of infants with RDS are deficient in pulmonary surfactant, the surface tension–reducing agent that prevents alveolar collapse and loss of lung volume at end expiration. Surfactant-deficient lungs develop progressive atelectasis,

which leads to intrapulmonary shunting, owing to perfusion of unventilated lung, and subsequent hypoxemia. The radiograph displays a characteristic ground glass, reticulogranular appearance with air bronchograms. When the lung inflation is poor due to stiff noncompliant lungs, the arterial blood gas analysis usually reveals respiratory acidemia as well as hypoxemia.

Therapy is directed toward improving oxygenation as well as maintaining optimal lung volume. Continuous positive airway pressure (CPAP) or PEEP is applied to prevent volume loss during expiration. In severe cases, mechanical ventilation via tracheal tube is required. Treatment with surfactant is the standard of care for preterm infants who require intubation for RDS. Exogenous surfactants (artificial and natural), which are available for intratracheal instillation, improve survival and reduce some of the associated morbidity of RDS. Earlier clinical trials indicated that prophylactic surfactant administration to extremely premature infants in the delivery room is more effective than waiting for the treatment after development of RDS (Soll & Morley, 2001). However, several subsequent trials, including the large SUPPORT trial in which prophylactic surfactant was compared to CPAP started at birth with rescue surfactant, showed equivalence, though many of the infants in the early CPAP arm ultimately required surfactant administration (Finer et al., 2010; Stetson, Brocklehurst, & Tarnow-Mordi, 2011). The most recent Cochrane review of the topic did not recommend routine administration of prophylactic surfactant administration, as there was less risk of BPD or death at 36 weeks when using early CPAP with selective surfactant administration for infants requiring intubation (Rojas-Reyes, Morley, & Soll, 2012). Prophylactic high-frequency ventilation for treatment of RDS has mixed results with limited evidence to support routine use (Cools, Offringa, & Askie, 2015), but these modes of ventilation should be considered as alternatives to conventional mechanical ventilation in specific circumstances such as in infants with air leaks including pulmonary interstitial emphysema or bronchopleural fistula. Infants greater than 34 weeks who have RDS and respiratory failure unresponsive to ventilatory management have responded favorably to extracorporeal membrane oxygenation (ECMO; Thome, Carlo, & Pohlandt, 2005).

Nursing care for infants with RDS is demanding; the most unstable infants often require a one-to-one, nurse-to-patient ratio. The nurse must monitor the quality of respirations and observe the degree of difficulty that the infant is experiencing. Worsening retractions may signal progressive volume loss and impending respiratory failure. **Quality and Safety: Arterial blood gas tensions and pH should be measured frequently, and continuous noninvasive monitoring of oxygenation, and carbon dioxide if available, may allow early identification of gas exchange problems.** The risk of pneumothorax and right mainstem intubation is high, and the symmetry of breath sounds must be verified regularly. A crying infant loses airway pressure when the mouth is open and therefore must be kept calm when receiving nasal CPAP. The intubated infant must be monitored for appropriate endotracheal tube position and patency. Suctioning of the airway should be done carefully. The suction catheter should be passed only as far as the end of the endotracheal tube because overzealous suctioning can denude the tracheal epithelium (Cordero, Sananes, & Ayers, 2000). Lung volume can be lost during prolonged disconnection from the ventilator. Rapid loss of lung volume can precipitate hypoxemia, so disconnection time should be minimized. Any sudden decompensation should alert the nurse to investigate for ventilator failure, pneumothorax, or tracheal tube plugging (Figure 6.4). The infant should also be closely monitored for changes in pulmonary compliance, especially after surfactant administration.

BPD is a common outcome in infants after RDS. BPD generally refers to a chronic lung disease in preterm infants characterized by pulmonary fibrosis, bronchiolar metaplasia, emphysema, and interstitial edema. It is most commonly seen in survivors of extreme prematurity who were diagnosed with RDS, but extremely low birth weight infants may develop BPD without a history of RDS. According to the National Institute of Child Health and Human Development (NICHD) consensus, infants with mild BPD are those who continue to require oxygen supplementation for a total of at least 28 days, while those with moderate or severe BPD require oxygen supplementation and/or ventilatory support at 36 weeks of postmenstrual age and for more than 28 days (Jobe & Bancalari, 2001). The incidence of BPD increases as gestational age decreases. Among infants less than or equal to 1,000 g at birth, 77% develop mild BPD, while 46% develop moderate BPD and 16% develop severe BPD (Ehrenkranz et al., 2005). Of survivors to 36 weeks corrected gestational age, 85% of infants born at 22 weeks had an oxygen requirement as opposed to 22% for infants born at 28 weeks (Stoll et al., 2010). Pulmonary morbidities and adverse neurodevelopmental outcomes at 18 to 22 months were more prevalent with an increased severity of BPD.

Several therapies reduce the incidence of BPD in preterm infants. A meta-analysis of the administration of vitamin A, an important mediator of pulmonary growth, showed a reduction in the incidence of BPD by 13% (Darlow & Graham, 2011). The administration of caffeine in the Caffeine for Apnea of Prematurity (CAP) trial found a reduction in BPD by 36% in infants who received caffeine compared with those receiving placebo. The administration of systemic corticosteroids after the first week of life reduces the incidence of BPD or BPD/death without causing any significant neurodevelopmental impairment (Doyle, Cheong, Ehrenkranz, & Halliday, 2017a), whereas giving steroids earlier (before 7 days of life) reduces BPD but with an increase in the incidence of cerebral palsy (Doyle, Cheong, Ehrenkranz, & Halliday, 2017b).

Air Leaks. Air leaks frequently complicate RDS and other neonatal respiratory disorders. Air leaks are characterized by air

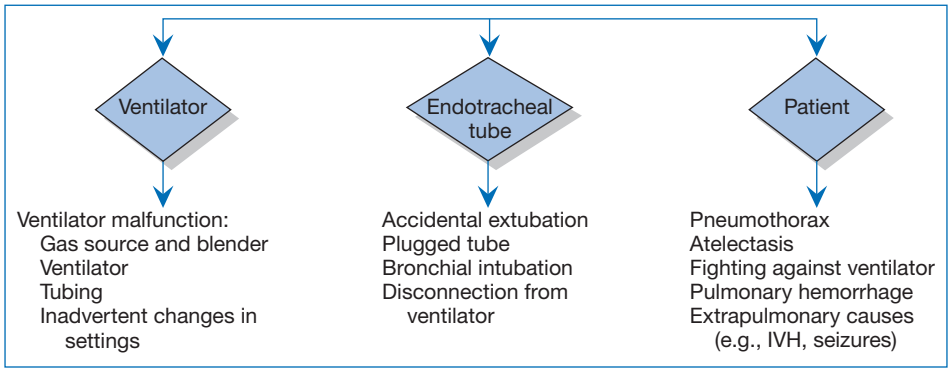

FIGURE 6.4 Acute deterioration in a ventilated patient.

IVH, intraventricular hemorrhage.

Box 6.3

AIR-LEAK PHENOMENA IN THE NEONATE

- Pneumothorax
- Pulmonary interstitial emphysema
- Pneumomediastinum
- Pneumopericardium
- Pneumoperitoneum
- Pulmonary venous air embolism
- Subcutaneous emphysema
- Pseudocyst

Source: From Battista, M. A., & Carlo, W. A. (1992). Differential diagnosis of acute respiratory distress in the neonate. *Tufts University School of Medicine and Floating Hospital for Children Reports on Neonatal Respiratory Diseases, 2*(3), 1–4, 9–11.

in an ectopic location (Box 6.3). Many air-leak syndromes begin with at least some degree of pulmonary interstitial emphysema, which is the result of alveolar rupture from overdistention, usually concomitant with mechanical ventilation at lower rates and longer inspiratory times (Greenough, Murthy, Milner, Rossor, & Sundaresan, 2016) or CPAP (Morley et al., 2008). Pulmonary interstitial emphysema occurs most commonly in preterm infants but may be seen in infants of any gestational age. Lung compliance is nonuniform, and areas of poor aeration and alveolar collapse may be interspersed with alveoli of normal or near-normal compliance. The more normal lung units (those with better compliance) become overdistended and eventually rupture. Air is forced from the alveolus into the loose tissue of the interstitial space and dissects toward the hilum of the lung, where it may track into the mediastinum—causing a pneumomediastinum—or into the pericardium—causing a pneumopericardium. **Emergency Alert: The astute clinician may notice that an infant's chest becomes barrel-shaped with overdistention and that breath sounds become distant on the affected side.** In contrast, the infant who suffers a pneumothorax usually becomes unstable, with development of cyanosis, oxygen desaturation, and carbon dioxide retention. The infant may become hypotensive and bradycardic because the high intrathoracic pressure impedes venous return. A tension pneumothorax, in which the free pleural air compresses the lung, is a medical emergency, and prompt relief by thoracentesis or tube thoracostomy is indicated. There are infants who are medically stable with a pneumothorax who can be managed expectantly without decompression (Litmanovitz & Carlo, 2008). However, it is important to ensure that these infants truly are medically stable and, if they deteriorate, to intervene when needed to relieve the pneumothorax.

Transient Tachypnea of the Newborn

TTN occurs typically in infants born by cesarean section, particularly in the absence of labor or in those infants born vaginally but who delivered precipitously. The cause of the disorder is thought to be transient pulmonary edema that results from decreased absorption of pulmonary alveolar fluid. The chest radiograph may show increased perihilar interstitial markings and small pleural fluid collections, especially in the minor fissure. In contrast to infants with RDS, infants with transient tachypnea tend to have a normal or low P_{CO_2}. Oxygenation can usually be maintained by supplementing oxygen with a hood, although some infants benefit from a short course of positive pressure support. The infant usually recovers in 24 to 48 hours. Restricting fluid intake may also help reduce the duration of respiratory support (Stroustrup, Trasande, & Holzman, 2012).

TABLE 6.2

CAUSES OF PNEUMONIA

Bacterial	Viral	Other
Group B Streptococcus	Cytomegalovirus	*Candida* and other fungi
Escherichia coli	Adenovirus	*Ureaplasma*
Klebsiella	Rhinovirus	*Chlamydia*
Staphylococcus aureus	Respiratory syncytial virus	Syphilis
Listeria monocytogenes	Parainfluenza	*Pneumocystis jiroveci*
Enterobacter	Enterovirus	Tuberculosis
Haemophilus influenzae	Rubella	
Streptococcus pneumonia		
Pseudomonas		
Bacteroides		
Others		

Source: Adapted from Battista, M. A., & Carlo, W. A. (1992). Differential diagnosis of acute respiratory distress in the neonate. *Tufts University School of Medicine and Floating Hospital for Children Reports on Neonatal Respiratory Diseases, 2*(3), 1–4, 9–11.

Pneumonia

Pneumonia may be of bacterial, viral, or other infectious origin (Table 6.2). Pneumonia may be transmitted transplacentally, as has been shown with group B *Streptococcus*, or via an ascending bacterial invasion associated with maternal chorioamnionitis and prolonged rupture of the membranes. The usual causative organisms of pneumonia are group B *Streptococcus*, *Escherichia coli*, *Haemophilus influenzae*, and, less commonly, *Streptococcus viridans*, *Listeria monocytogenes*, and anaerobes.

A strong association exists between bacterial pneumonias and premature birth, which may be due to a developmental deficiency of bacteriostatic factors in the amniotic fluid. Alternatively, the infection may be a precipitating factor in preterm labor. Chorioamnionitis can occur even in the presence of intact membranes. Blood cultures and other diagnostic tests are necessary to help

direct specific antimicrobial therapy. The clinician should be attuned to the labor history. Were membranes ruptured for more than 12 to 24 hours? Did the mother have fever before delivery? Did the mother receive intrapartum antibiotics if risk factors for group B *Streptococcus* sepsis were present? Elements of the maternal history that delineate isolated maternal fever from a suspected intraamniotic infection include maternal leukocytosis, purulent cervical discharge, and fetal tachycardia (Committee on Obstetric Practice, 2017). The full-term infant who exhibits tachypnea, grunting, retractions, or temperature instability should be evaluated carefully. Although blood counts may be helpful as low white blood cell counts, low neutrophil counts, and high immature to total neutrophil ratios are associated with a higher odds of infection, these are imperfect predictors and should not solely be used to rule out infection (Hornik et al., 2012). Infection should be considered in any newborn with respiratory distress or more than transient oxygen requirements. Tracheal aspirates obtained within 8 hours of birth and that show both bacteria and white blood cells on Wright's stain are highly predictive of pneumonia.

Pending culture results, treatment is usually begun with broad-spectrum antibiotics, typically a penicillin and aminoglycoside or cephalosporin. A lumbar puncture may be undertaken or may be postponed until results of blood culture are obtained. When cultures result in the identification of the organism, the study of antibiotic sensitivity allows the clinician to identify the most effective antibiotic or combination of antibiotics for the causative agent. Antibiotic treatment for up to 10 to 14 days may be necessary.

Persistent Pulmonary Hypertension of the Newborn

Persistent pulmonary hypertension of the newborn (PPHN), or persistent fetal circulation, is a term applied to the combination of pulmonary hypertension (high pressure in the pulmonary artery), subsequent right-to-left shunting through fetal channels (the foramen ovale or ductus arteriosus) away from the pulmonary vascular bed, and a structurally normal heart. The syndrome may be idiopathic or, more commonly, secondary to another disorder—such as MAS, congenital diaphragmatic hernia (CDH), RDS, asphyxia, sepsis, pneumonia, hyperviscosity of the blood, or hypoglycemia (Walsh-Sukys et al., 2000). Idiopathic causes may be related to maternal late trimester nonsteroidal anti-inflammatory drug use or maternal use of selective serotonin reuptake inhibitors (Dhillon, 2011).

The neonatal pulmonary vasculature is sensitive to changes in Pa_{O_2} and pH and, during stress, can constrict to cause increased pressure against which the neonatal heart cannot force blood flow to the lungs. If the pulmonary artery pressure is higher than systemic pressure, blood flows through the path of least resistance, away from the lungs through the foramen ovale and the ductus arteriosus. The infant becomes progressively hypoxemic and acidemic, which accentuates the problem of increased pulmonary vascular resistance.

Management of infants with PPHN demands high vigilance. Because the pulmonary vasculature is unstable, almost any event can precipitate severe hypoxemia, including routine procedures such as endotracheal tube suctioning, weighing, positioning, and diaper changes. Under these circumstances, minimal stimulation is usually practiced.

Occasionally, sedation, and even muscle paralysis, is necessary to prevent spontaneous episodes of hypoxemia or deterioration associated with procedures (e.g., suctioning and position changes). Mild alkalosis—either with bicarbonate infusion or by mild hyperventilation—often relaxes the pulmonary vascular bed and allows better pulmonary perfusion and thus oxygenation. The approach to therapy should be directed toward preventing hypoxemia and acidosis. The critical pH necessary for overcoming pulmonary vasoconstriction seems to be unique to the individual. High applied ventilator pressures predispose the lung to air-leak syndromes, further increasing the risk of sudden destabilization. Vasopressor therapy with dopamine and dobutamine is often used in conjunction with hyperventilation, but controlled data are not available. Presumably, they act both to improve contractility of the stressed myocardium, which improves CO, and to raise systemic arterial pressure above pulmonary artery pressure to reduce right-to-left shunting.

When conventional therapies fail, high-frequency ventilation may be attempted. Approximately 30% to 60% of patients who fail conventional mechanical ventilation respond to high-frequency ventilation. However, the exact role of high-frequency ventilation in mortality or in preventing the need for ECMO needs further evaluation. Since the early 1990s, inhalation of nitric oxide—alone and in association with high-frequency ventilation—has been shown to be an effective therapy for PPHN (Davidson et al., 1998; Finer & Barrington, 2006; The Neonatal Inhaled Nitric Oxide Study Group, 1997).

When oxygenation cannot be accomplished despite the use of conventional mechanical ventilation, high-frequency ventilation, or nitric oxide, ECMO has proven to be an effective therapy (UK Collaborative ECMO Trial Group, 1996). Neonatologists disagree about the exact indications for ECMO, and some centers report impressive survival statistics without the use of ECMO (Mok, Yates, & Tasker, 1999). However, ECMO often is the only treatment that improves the outcome of some infants who fail less invasive therapies.

Meconium Aspiration Syndrome

MAS is the most common aspiration syndrome that causes respiratory distress in neonates. The role of meconium in the pathophysiology of aspiration pneumonia has become controversial. It is unclear whether the material itself causes pneumonitis severe enough to lead to hypoxemia, acidosis, and pulmonary hypertension or whether the presence of meconium in the amniotic fluid is merely a marker for other events that may have predisposed the fetus to severe pulmonary disease. The severely ill infant with MAS typically comes from a stressed labor and has depressed cord pH from metabolic acidosis. These infants are often postmature and exhibit classic signs of weight loss, skin peeling, and deep staining of the nails and umbilical cord. Pharyngeal suctioning at the time of birth does not reduce MAS (Vain et al., 2004). Guidelines for the resuscitation of non-vigorous infants with meconium-stained fluid were revised in 2015 and no longer include rapid intubation and suctioning of the airway (Wyckoff et al., 2015). This change in clinical practice was due to concerns for the potential for delay in bag mask ventilation in these infants without any known benefit and possible harm of endotracheal suctioning as randomized controlled trials showed no benefit of routine endotracheal suctioning in non-vigorous newborns (Chettri, Adhisivam, & Bhat, 2015; Nangia, Sunder, Biswas, & Saili, 2016). Additionally, suctioning the mouth and nose provides no benefit compared to wiping the mouth as part of routine resuscitation (Kelleher et al., 2013).

Pulmonary disease in infants with MAS arises from chemical pneumonitis, interstitial edema, small airways obstruction, and from concomitant persistent pulmonary hypertension. The infant may have uneven pulmonary ventilation with hyperinflation of some areas and atelectasis of others, leading to ventilation–perfusion mismatching and subsequent hypoxemia. The hypoxemia may then exacerbate pulmonary vasoconstriction, leading to deeper hypoxemia and acidosis. Infants with MAS may have evidence of

lung overinflation with a barrel-chested appearance. Auscultation reveals rales and rhonchi. The radiograph shows patchy or streaky areas of atelectasis and other areas of overinflation.

As with other cases of pulmonary hypertension, nursing care of infants with MAS centers on maintenance of adequate oxygenation and acid–base balance and on the avoidance of cold stress, which contributes to acidosis. A high incidence of air leaks exists in these infants, and positive pressure ventilation is best avoided if the patient can be adequately oxygenated, even at very high-inspired oxygen concentrations. Antibiotics are often used, particularly in critically ill infants, at least until a bacterial infection is ruled out, but antibiotic therapy may not be necessary. The infant is often exquisitely sensitive to environmental stimuli and should be treated in as quiet an environment as possible. Interventions should be preplanned to maximize efficiency of handling the infant. Infants with very severe respiratory failure and MAS improve with the administration of exogenous surfactant as aspiration may lead to secondary surfactant deficiency (El Shahed, Dargaville, Ohlsson, & Soll, 2007).

Although aspiration of meconium is most common, the neonate may become symptomatic as a result of the aspiration of blood, amniotic fluid, or gastrointestinal contents. The history is important in the differential diagnosis because radiographs are nondiagnostic.

Pulmonary Hemorrhage

Pulmonary hemorrhage is rarely an isolated condition and usually occurs in an otherwise sick infant. RDS, asphyxia, congenital heart disease, aspiration of gastric content or maternal blood, and disseminated intravascular coagulation and other bleeding disorders may play a role in the cause of pulmonary hemorrhage. The presence of a patent ductus arteriosus increases the risk for a clinically significant pulmonary hemorrhage that requires increased respiratory support and/or blood products. The administration of prophylactic indomethacin reduces the risk for clinically significant pulmonary hemorrhage by 35% (Alfaleh et al., 2008). The risk for pulmonary hemorrhage is increased by approximately 5% in infants receiving either natural or artificial surfactant. Massive bleeding may also occur as a complication of airway suction secondary to direct trauma of the respiratory epithelium.

Pulmonary hemorrhage is manifested by the presence of bloody fluid from the trachea. **Emergency Alert: When massive, it may be heralded by a sudden deterioration with pallor, shock, cyanosis, or bradycardia.** Attention must be given to maintenance of a patent airway because an obstructed endotracheal tube requires emergency replacement. However, replacing an occluded airway in the context of a massive pulmonary hemorrhage should be undertaken with caution as the bleeding can make visualization of the trachea difficult. Although studies have been reported describing the benefits of administration of surfactant in neonates with pulmonary hemorrhage, there are no high level of evidence studies to support its use (Aziz & Ohlsson, 2012). Suctioning must be done with great care to avoid precipitation of further bleeding. Clotting factors can be consumed rapidly, and the nurse should be alert to signs of generalized bleeding.

Pleural Effusions

Pleural effusions may be caused by accumulation of fluid between the parietal pleura of the chest wall and the visceral pleura enveloping the lung. A pleural effusion may also be due to chylothorax (lymphatic fluid) or hemothorax (blood). Lymphatics drain fluid that filters into the pleural space. Fluid accumulates in the pleural space as a result of either increased filtration or decreased absorption. An increase in filtration pressure, as seen with increased venous pressure in hydrops fetalis or congestive heart failure, leads to pleural effusion. The rate of filtration into the pleural space also increases if the pleural membrane becomes more permeable to water and protein, as occurs with infection.

Pleural effusion with high glucose content in an infant who is receiving parenteral nutrition via a central venous catheter should raise the suspicion of catheter perforation into the pleural space. If the infant is also receiving lipid infusion, the fluid may appear milky and be confused with chylothorax.

Chylothorax may be either congenital or acquired. Congenital chylothorax frequently presents at delivery or shortly after with respiratory distress. Chylothorax can also be acquired as a surgical complication of repair of diaphragmatic hernia, tracheoesophageal fistula, or congenital heart defect. Congenital chylothorax may be suspected in the infant who cannot be ventilated in the delivery room. Breath sounds are difficult to hear, and chest movement with ventilation is minimal. Bilateral thoracenteses may be lifesaving. The typical pleural fluid in a chylothorax—opalescent and rich in fat—is present only if the infant has been fed. Therefore, the fluid aspirated in the delivery room or shortly after birth in a child with congenital chylothorax often has a low triglyceride level.

Pleural effusions that impede respiratory function typically require drainage by thoracentesis or tube thoracostomy. It may be necessary for chest tubes placed for chylothorax and thoracic duct injury to remain in place for extended periods while the infant is given total parenteral nutrition, receiving nothing by mouth, thus minimizing thoracic duct flow. Somatostatin administration (such as octreotide) has been associated with a reduction in need for ventilator support (Yin et al., 2017). Several commercial formulas containing a higher percentage of medium-chain triglycerides that bypass the lymphatic system are also available for infants transitioning off parenteral nutrition. Due to the loss of lymphocytes and immunoglobulins through chylous drainage, these infants may also become immunocompromised and may benefit from immunoglobulin replacement.

Apnea

Apnea is the common end product of a myriad of neonatal physiologic events. Hypoxemia, infection, anemia, thermal instability, metabolic derangement, drugs, and intracranial disease can cause apnea. These causes should be considered before idiopathic apnea of prematurity is diagnosed.

Apnea is observed in more than half of surviving premature infants who weigh less than 1.5 kg at birth. The respiratory control mechanism and central responsiveness to carbon dioxide is progressively less mature the lower the gestational age. In contrast to adults, infants respond to hypoxemia with only a brief hyperpneic response followed by hypoventilation or apnea. In any infant who has apnea, hypoxemia should always be ruled out before the clinician embarks on any other workup or institutes therapy.

Care of the infant experiencing apneic episodes requires close observation. Obstructive apnea cannot be detected with the impedance respiratory monitor because normal or pronounced respiratory excursions of the chest wall exist. Prompt tactile stimulation for mild "spells" is often sufficient to abort the episode of apnea, obviating the need for further therapy. Infants with apneic episodes accompanied by profound bradycardia need prompt attention to their immediate needs as well as more aggressive diagnostic and therapeutic intervention.

Sensory stimulation with waterbeds or other means can sometimes be used to manage these infants, particularly those with mild apnea. Many apneic neonates respond to nasal CPAP at low pressures because the majority of apneic episodes have an obstructive component. Pressure support may also stimulate pulmonary stretch receptors, thus stimulating respiration. Nursing care that is directed toward promoting a neutral thermal environment, normoxia, optimal airway maintenance, and prevention of aspiration is essential in the care of neonates at risk for apnea.

Use of methylxanthines, such as caffeine and aminophylline, has markedly simplified the treatment of apnea in some premature infants. Xanthines appear to exert a central stimulatory effect on brainstem respiratory neurons and often markedly decrease the frequency and severity of apneic episodes. The clinician must be attuned to the toxicities of xanthines, including tachycardia, excessive diuresis, and vomiting. Caffeine may be associated with a lower risk of adverse effects (Schmidt et al., 2006). The timing of caffeine initiation as well as optimal dosing in preterm infants remains controversial. Little evidence supports early administration of caffeine (within 36 hours of birth) with the possibility of harm. The use of higher caffeine doses later on (i.e., in the setting of extubation) may confer neurodevelopmental benefit (Gentle, Travers, & Carlo, 2018; Gray, Flenady, Charles, & Steer; Caffeine Collaborative Study Group, 2011).

CONGENITAL ANOMALIES THAT AFFECT RESPIRATORY FUNCTION

Diaphragmatic Hernia

CDH occurs at a frequency of 1 in 2,500 live births and may be unsuspected until birth. Herniation of abdominal contents into the chest cavity early in gestation is accompanied by ipsilateral pulmonary hypoplasia. By mechanisms that are not well understood, there is often some degree of pulmonary hypoplasia on the contralateral side as well. Most infants are symptomatic at birth, with severe respiratory distress in the delivery room. The affected newborn's abdomen is usually scaphoid, and breath sounds are absent on the side of the defect (a left-sided defect occurs in 90% of cases). Bowel sounds may be heard in the chest, and heart sounds may be heard on the right side because the herniated abdominal contents push the mediastinum to the right.

Quality and Safety: As soon as the diagnosis is suspected, bag and mask ventilation should be avoided because it fills the herniated intestinal contents with gas, which can lead to further lung compression and worsening ventilation. When CDH has been diagnosed prenatally, the infant should be intubated and mechanical ventilation should be initiated immediately after birth. An orogastric tube should be placed to aid in decompression of the herniated abdominal viscera. Ventilation should be attempted with a rapid rate and low inflation pressure while tolerating hypercapnia. Symptomatic neonates often have pulmonary hypertension and progressive right-to-left shunting. Hypotension is common, and, when adequate intravascular volume is established, dopamine infusion may be helpful. Studies of inhaled nitric oxide have shown limited evidence for effectiveness in the treatment of diaphragmatic hernia (Finer & Barrington, 2006). Although evidence of surfactant deficiency in these newborns exists, surfactant administration does not appear to improve their clinical course or outcome (Colby et al., 2004).

The use of ECMO, more commonly required in infants with liver herniation or smaller lung volumes, may not lead to improvement in survival (Zalla, Stoddard, & Yoder, 2015). Surgery to repair the defect is indicated. Controversy regarding the urgency of the procedure exists among pediatric surgeons, and some prefer to stabilize the patient with mechanical ventilation, vasopressors, and correction of acidosis before undertaking surgical intervention; others perform surgical repair while the patient is maintained on ECMO.

Congenital Heart Disease

Congenital heart disease commonly manifests with signs of respiratory distress. Neonates with congenital heart disease who demonstrate right-to-left shunting and decreased pulmonary blood flow (e.g., tetralogy of Fallot, pulmonary valve atresia, and tricuspid valve atresia or stenosis) usually present with profound cyanosis unresponsive to oxygen supplementation. Neonates with congenital heart disease who demonstrate increased pulmonary blood flow or obstruction to the left outflow tract (e.g., transposition of the great vessels, total anomalous pulmonary venous return, atrioventricular canal, hypoplastic left heart syndrome, and critical coarctation of the aorta) may transiently improve with oxygen supplementation. However, oxygen supplementation in some conditions such as hypoplastic left heart syndrome can worsen systemic flow and make the child worse. Neonates with noncyanotic lesions such as patent ductus arteriosus and ventricular septal defect may present with signs of congestive heart failure (see Chapter 7, Cardiovascular System).

Choanal Atresia

Choanal atresia causes upper airway obstruction in the neonate. The choanae, or nasal passages, are separated from the nasopharynx by a structure known as the bucconasal membrane, which normally perforates during gestation. Failure of this developmental event results in an obstructed airway, occurring bilaterally in 50% of cases. Most affected infants are female and half of the affected infants have associated anomalies such as CHARGE (coloboma, heart defects, atresia of the choanae, retardation of growth and development, genital and urinary abnormalities, and ear abnormalities and/or hearing loss) syndrome. Because newborns are obligate nasal breathers, they have chest retractions and severe cyanosis (particularly during feeding), and paradoxically turn pink when crying. Diagnosis can be made via nasal endoscopy; however, CT imaging is also typically performed. Emergency treatment consists of tracheal intubation or placement of an oral airway. Surgical correction is indicated, though the ideal surgical intervention remains unclear (Cedin, Atallah, Andriolo, Cruz, & Pignatari, 2012). In cases where atresia is bilateral, surgery usually occurs in the first week after birth.

Cystic Hygroma

A variety of space-occupying lesions can impose on the airway of the newborn (Box 6.4). Most are derived from embryonic tissues. Cystic hygroma, derived from lymphatic tissue, is the most common lateral neck mass in the newborn. It is multilobular, multicystic, and, when large, obstructs the airway. Surgery is curative, although it is sometimes technically difficult. The clinician must always be mindful of the airway and its patency. Many of these lesions are of great cosmetic concern and cause great distress in the parents. A care plan should address these parental concerns. It is sometimes helpful to facilitate contact with parents of other children with similar problems who can share similar experiences.

Pierre Robin Sequence

The major feature of Pierre Robin sequence is micrognathia (a small mandible). The tongue is posteriorly displaced into the oropharynx, thus obstructing the airway. Sixty percent of affected patients also

Box 6.4

THORACIC CYSTS AND TUMORS THAT MAY CAUSE RESPIRATORY DISTRESS IN THE NEONATE

- Teratoma
- Cystic hygroma
  - Neurogenic tumor
  - Neuroblastoma
  - Ganglioneuroma
  - Neurofibroma
- Bronchial or bronchogenic cyst
- Intrapulmonary cyst
- Gastrogenic cyst
- Hemangioma
- Angiosarcoma
- Mediastinal goiter
- Thymoma
- Mesenchymoma
- Lipoma
- Cystic adenomatous malformation

Source: Adapted from Battista, M. A., & Carlo, W. A. (1992). Differential diagnosis of acute respiratory distress in the neonate. *Tufts University School of Medicine and Floating Hospital for Children Reports on Neonatal Respiratory Diseases, 2*(3), 1–4, 9–11.

have a cleft palate. Obstructive respiratory distress and cyanosis are common and may be severe. In an emergency, as with all airway obstructions (obstructive apnea), tracheal intubation should be undertaken. Infants with Pierre Robin sequence are nursed in the prone position to prevent the tongue from falling backward. Nasogastric tube feedings are usually required in the neonatal period. With good care, the infant has a good prognosis for survival; the mandible usually grows; and the problem resolves by 6 to 12 months of age. Some infants will require surgical intervention if positioning changes do not enable an infant to successfully feed by mouth or prevent apneic symptoms. Surgical correction includes mandibular distraction or tongue to lip adhesion, both of which have reduced or eliminated the need for tracheostomy (Khansa et al., 2017).

COLLABORATIVE MANAGEMENT OF INFANTS WITH RESPIRATORY DISORDERS

Supportive Care

Supportive care of the infant in respiratory distress requires attention to detail. The clinicians' primary goals are to minimize oxygen consumption and carbon dioxide production. These goals are accomplished by maintaining a neutral thermal environment. The nurse must be skilled in physical assessment to interpret signs and symptoms, such as cyanosis, gasping, tachypnea, grunting, nasal flaring, and retractions. By understanding the pathophysiology of breathing, the nurse knows that the infant with retractions has decreased lung compliance and that the cyanotic infant has poor tissue oxygenation.

Excellent communication is needed between the neonatal nurse and the rest of the neonatal team. Acutely ill neonates with respiratory disease are often unstable and their condition can deteriorate rapidly, so astute observation skills are necessary. Assessment is a continuous process, and effective communication among nurses, respiratory therapists, physicians, and support staff is necessary for proper delivery of intensive care. The nurse, who is the primary bedside caregiver, is the gatekeeper for all interactions between the patient and the environment. The nurse who is caring for an unstable patient should be the patient's advocate, whether such a role involves regulating the timing of a physical examination by the physician or venipuncture for laboratory investigation.

Technical competence is an important facet of the nurse's repertoire. The nurse is responsible for maintaining intravenous lines and tracheal tube patency, accurately measuring volumes of intravenous intake as well as urinary output, and operating advanced electronic machinery. Moreover, the nurse must also be adept at interpreting arterial blood gas and laboratory data in order to communicate these to the rest of the care team and to develop a cogent management plan. Many functions are shared to some degree with respiratory therapists. Whether nurses or respiratory therapists make ventilator changes, the nurse should become familiar with the effects of ventilator setting changes on blood gases. $PaCO_2$ is affected by changes in ventilator rate and tidal volume. Tidal volume depends on the difference between PIP and PEEP. Thus, to decrease $PaCO_2$, either rate or inspiratory pressure should be increased. PaO_2 depends on the fraction of inspired oxygen concentration (FiO_2) and mean airway pressure (MAP). MAP depends on PIP, PEEP, inspiratory to expiratory time ratio, and gas flow. To improve PaO_2, the most effective changes are to increase MAP by increasing PIP or PEEP or to increase FiO_2. The nurse should also be familiar with ventilator functioning so that malfunctions can be detected promptly. The nurse should always be prepared to bag-ventilate an intubated neonate in the event that decompensation occurs while the status of the ventilatory apparatus is checked. Nurses and therapists often share such functions as airway suctioning, monitoring and recording of inspired oxygen concentration, and delivery of chest physical therapy.

The delivery of oxygen therapy should always be carefully monitored. Desired oxygenation parameters should be recorded in the nurse's notes and followed using continuous pulse oximetry and measurement of arterial blood gases as indicated. The acutely ill infant should have FiO_2 measured continuously and recorded frequently. The goal for oxygenation depends on the patient's diagnosis and condition. For example, in infants with PPHN, an apparently acceptable saturation may occur despite marked right-to-left shunting. In preterm infants, oxygen saturation should be kept in the low 90s, thus avoiding the risks associated with hyperoxia or hypoxemia. Large randomized controlled trials (e.g., Carlo et al., 2010; Schmidt et al., 2013; Stenson et al., 2013) and meta-analyses (e.g., Askie et al., 2017, 2018) indicate that targeting lower oxygen saturations (85%–89%) versus higher saturations (91%–95%) in extremely preterm infants less than 28 weeks' gestation increases mortality and necrotizing enterocolitis without decreasing blindness. Targeting different saturations does not result in differences in neurodevelopmental impairment. Thus, targeting 91% to 95% or 90% to 95% oxygen saturations as others have suggested is now recommended by most experts to reduce mortality and necrotizing enterocolitis in extremely preterm infants.

Airway suctioning is a procedure that may be associated with cardiopulmonary derangement, hypoxemia, bradycardia, and hypertension. Various techniques to perform airway suctioning exist—including preoxygenation (increase in FiO_2 before the procedure), normal saline instillation before the suctioning to improve secretion aspiration, and the use of a closed system to avoid disconnection from the ventilator. The nurse should become familiar with the

techniques used in the NICU and be aware of the associated complications. Suctioning of the airway should be done only as often as necessary to remove pulmonary secretions that could occlude the airway. The suction catheter should be passed no further than the end of the tracheal tube because epithelium is easily damaged. There is perhaps little need to vigorously suction the intubated infant with RDS in the first days after birth because secretions are minimal and lung volume is lost with every disconnection of the ventilator circuit.

The sudden decompensation of a ventilated infant should alert the nurse to assess disconnection of the ventilator, pulmonary air leak, ventilator failure, or obstructed tracheal tube (see Figure 6.4). The very small infant who suddenly decompensates may have experienced a severe intracranial hemorrhage.

Care of the infant who is receiving CPAP can be particularly challenging. These infants should be kept calm and swaddled if necessary. Crying releases pressure through the mouth; thus, lung volume is lost. Nasal CPAP is effective, but particular attention must be given to maintaining patency of the nose, the nasal prongs, and the pharynx. The infant's nares and nasal septum should be guarded from pressure necrosis from inappropriately applied prongs. The infant with respiratory disease must be constantly assessed for airway patency. If the infant is unable to grunt against a closed glottis and maintain positive airway pressure, the condition may worsen if airway pressure is not maintained properly. Vibration and percussion should be used judiciously in the infant with pulmonary secretions to loosen them and allow removal via suction.

ASSESSMENT AND MONITORING

The most important aspect in monitoring patients with respiratory disease is the close and continuous observation of signs and symptoms. The color of the patient gives important clues. An infant with pink lips and oral mucosa has good oxygenation and perfusion; a cyanotic patient has poor tissue oxygenation. If the hemoglobin concentration is too low, the patient can be hypoxemic, but because the concentration of deoxyhemoglobin is low, there may be no cyanosis. An infant with tachypnea and retractions usually has decreased lung compliance. A patient with a barrel-shaped thorax, taking deep breaths, and with a normal or low respiratory rate probably has an increased airway resistance and gas trapping. Observation of the intubated patient is especially important. An anguished infant, who is cyanotic and breathing deeply, may have an obstructed endotracheal tube. An infant with RDS and increased chest expansion over time, despite no change in ventilatory pressure, is experiencing improvement in lung compliance. The same infant with later asymmetry in chest and sudden deterioration of oxygenation may have a pneumothorax. Cardiac beats, easily seen through the thoracic wall, may be caused by the presence of a symptomatic patent ductus arteriosus. A recently extubated infant, in whom increased retractions and inspiratory stridor develop, probably has upper airway obstruction. Auscultation helps in the diagnosis of increased airway resistance or the presence of secretions. It also allows the clinician to assess the response to different treatment maneuvers, such as suctioning, chest physiotherapy, and bronchodilation. Asymmetries in auscultation suggest mainstream bronchial intubation, atelectasis, pneumothorax, or pleural effusion.

Great progress has been made in noninvasive monitoring of blood gas tensions, but blood sampling is still necessary for pH determination and arterial samples are preferable. Capillary specimens are undependable, especially for Po_2. If peripheral perfusion is adequate, capillary blood approximates arterial values of pH and Pco_2. However, capillary blood Po_2 values do not reliably reflect arterial oxygenation.

Neonatal care has changed dramatically with the advent and widespread use of transcutaneous monitoring of Pao_2, $Paco_2$, and Sao_2. The neonatal intensive care team should become familiar with the devices used in noninvasive gas monitoring. Knowing the basis for their functioning as well as how to interpret the information they provide and being aware of clinical situations in which the information provided is not reliable or needs to be complemented before any management decisions are made is essential.

Transcutaneous Po_2 ($TcPo_2$) is measured with an electrode that is applied over the skin and heated to 42°C to 44°C. The electrode measures skin Po_2, not arterial Po_2. Skin Po_2 measurement depends on skin perfusion and on oxygen diffusion across the epidermis. Warming the skin to 42°C to 44°C under the electrode increases skin perfusion so that $TcPo_2$ correlates better with arterial Po_2. For initiation of $TcPo_2$ monitoring, 10 to 15 minutes are needed to obtain a stable reading. Thereafter, $TcPo_2$ reflects changes on Fio_2 with a 10- to 20-second delay. After 4 to 6 hours, the method becomes unreliable because of changes in skin secondary to hyperthermia, so the electrode position should be changed. In premature infants with more labile skin, the electrode placement should be changed even more frequently to avoid skin burns. The nurse should be aware of situations that make $TcPo_2$ lose its reliability. Overestimation of oxygenation occurs when an air bubble or leak between the electrode and the skin occurs or when the calibration is improper. Underestimation occurs with skin hypoperfusion, in older infants (increased thickness of the skin), with insufficient heating of the electrodes, or with improper calibration.

$TcPo_2$ monitoring has been largely supplanted by continuous pulse oximetry. Arterial oxygen saturation is computed from absorption of emitted low-intensity red or infrared light. The probe is attached to a finger or toe in large infants or to a hand or foot in small premature infants. Pulse oximetry offers the following advantages over transcutaneous oxygen monitoring: (a) avoidance of heating the skin and the risk of burns; (b) elimination of a delay period for transducer equilibration; (c) accurate measurement regardless of the presence of edema or patient age; (d) in vitro calibration not required; and (e) frequent position changes not required. However, the nurse should be aware that Sao_2 higher than 97% may be associated with Pao_2 higher than 100 mmHg. This is important in premature infants who are at risk for retinopathy of prematurity. Sao_2 between 90% and 95% probably is associated with a safe range of Pao_2. With Sao_2 over 95% to 97% and especially when it is 100%, the clinician cannot predict a patient's Pao_2. When the saturation is 100%, the Pao_2 can be approximately 100 mmHg or much higher (see Figure 6.1). This situation is particularly important in infants with PPHN because the decision whether to wean ventilator settings depends on Pao_2. In these patients, the simultaneous use of $TcPo_2$ and pulse oximetry is a useful alternative.

A common problem of pulse oximetry is the presence of motion artifact, an altered signal caused by movement of the part of the body where the sensor is applied. Because the pulse waveform is not detected, this movement is recognized by the loss of correlation between the oximeter pulse rate and the electrical monitor heart rate. With current technology the motion artifacts have been minimized (Malviya et al., 2000). Peripheral pulse oximetry may not detect pulse signals in patients with hypotension and poor perfusion. $TcPo_2$ may also give false readings in this situation. The clinician should be aware that pressure of the probe over the skin can produce skin pressure necrosis. This consideration is particularly important in the premature infant. Phototherapy may interfere with accuracy of Sao_2 monitoring, but this problem can be avoided by covering the sensor with an opaque material (e.g., a diaper).

Pulse oximetry is now the standard of care in the NICU. Additional $TcPo_2$ monitoring may be useful in several clinical

situations. They may be used in neonates with mild respiratory distress, such as transient tachypnea, to assess the oxygen requirement and to allow weaning without placement of an arterial catheter. In infants receiving mechanical ventilation, $TcPo_2$ or pulse oximetry helps to assess the effects of ventilator setting changes, thus reducing the need for arterial blood sampling. Continuous oxygenation monitoring reduces the risk of hyperoxemia or hypoxemia during interventions such as airway suctioning, position change, lumbar puncture, or venous cannulation. This monitoring is particularly helpful in the care of infants who do not tolerate excessive stimulation, such as those with PPHN. $TcPo_2$ and pulse oximetry monitoring are also useful in caring for patients with PPHN because simultaneous monitoring of preductal (head, right arm, right upper chest) and postductal (left arm, abdomen, legs) $TcPo_2$ or Sao_2 allows assessment of the magnitude of ductal shunting or the response to therapies such as vasodilation or alkalinization.

Transcutaneously measured Pco_2 is accomplished with a glass electrode that is pH-sensitive. Transcutaneous Pco_2 response is slower than that of $TcPo_2$, and the value measured must be corrected for skin production of carbon dioxide. Thus, transcutaneously measured values are approximately 1.3 to 1.4 times higher than arterial Pco_2 values. Most modern monitors display an electronically corrected value to $TcPo_2$. This modality is especially useful for monitoring chronically ventilated patients without indwelling catheters and also to reduce the number of laboratory tests in infants with indwelling catheters. Blood gas values during arterial puncture or vigorous crying during the procedure are often affected by breath holding and shunting and thus may be misleading.

ENVIRONMENTAL CONSIDERATIONS

Maintenance of the therapeutic environment is an important nursing function. Much attention has been given recently to the effects of sensory stimulation on the infant with respiratory distress. The sick newborn often has unstable pulmonary vasculature and may be particularly prone to hypoxic vasoconstriction. This phenomenon may be triggered in some individuals by excess stimulation, such as loud noise, handling, or venipuncture. It has been shown that the agitated neonate has more difficulty with oxygenation and that a quiet, minimally stimulating environment allows for more stable oxygenation (Als, 1998). The nurse should develop a care plan that allows the baby long periods of undisturbed rest by clustering interventions into short periods whenever possible. Positioning the infant in the flexed or fetal position or "nesting" may help in calming some infants. Always watch for stress cues to see how the infant is tolerating the care. Clustering of care only works if the infant tolerates a longer period of care rather than episodic care. Either way the infant needs undisturbed periods where rest and recovery can occur.

FAMILY CARE

Neonates with respiratory distress frequently require multiple instrumentations. They are typically in an incubator and may have endotracheal tubes, umbilical catheters, oximeter probes, chest leads, and other paraphernalia attached or applied to the skin. All of these interventions can give parents a feeling of increased separation from the infant. The nurse should explain the equipment surrounding the bedside as well as the function of invasive catheters, monitoring leads, and tracheal tubes. Terminology appropriate to the parents' level of understanding should be used. Even the most astute parents may be bewildered, and repetition is necessary. Staff should maintain consistent terminology so that the parents do not become confused between "respirators" and "ventilators." Whenever possible, the use of frightening or inaccurate terms should be avoided. Imagine the fear engendered by the phrase, "We paralyzed your baby last night."

Parents should be involved in developing and implementing the plan of care as much as possible. The mother who plans to breastfeed can be assisted in pumping her breasts and freezing the milk, even if enteral feedings are delayed for some time. This pumping may be the only thing that she alone can do for her baby.

Often lost in the bustle of critical care is the need for privacy. The perceptive nurse senses this need and backs away from the bedside when appropriate, allowing the parent some time with the infant. Care of the neonate requires a team—a coordinate team and that includes the parents!

SUMMARY

Most infants admitted to the NICU present with breathing difficulty. Nursing care of these infants requires a broad knowledge of newborn physiology and practical skills in the application of therapies that are directed toward solving the many problems that sick infants can have. The nurse often must anticipate these problems. While managing the nursing care for several patients, the neonatal nurse must also care for the sickest of infants. Parents and families of all infants in the NICU require special attention not only to achieve an understanding of the complex issues surrounding the infant's illness but also to calm fears and guilt that are often experienced. The rewards of being part of the accomplishments in the NICU may be overlooked as they are usually slowly achieved. However, when they are recognized, the victories surpass the greatest of expectations.

CASE STUDY

■ **Identification of the Problem.** A term infant was admitted to the NICU. The infant developed respiratory distress soon after birth. Birth weight was 4,000 g. Since birth, the infant had an increasing oxygen requirement and because of a recent desaturation episode, he is now receiving 100% oxygen on a ventilator. The ventilatory settings are PIP of 25 cm H_2O, PEEP of 5 cm H_2O, ventilator rate 60 per minute, and inspiratory time 0.4 seconds. A recent blood gas showed a pH of 7.35, Pco_2 of 42, Po_2 of 60, and bicarbonate of 22.

■ **Assessment: History and Physical Examination.** The infant was born by emergency C-section because of late decelerations and thick meconium-stained fluid. No signs of infection were observed. His mother had gestational diabetes and was maintained on insulin. The infant was not vigorous at birth and received bag mask ventilation at birth as endotracheal suction is no longer recommended. Blow-by oxygen was then administered and the infant responded well, initially weaned to 40% oxygen. However, after transfer to the NICU, he had increasing oxygen requirements.
The physical examination is now pertinent for excellent chest rise, equal breath sounds, central cyanosis with oxygen saturations in the mid-80s, good color and perfusion, and normal tone and reflexes.

■ **Differential Diagnosis.** Many conditions should be considered in the differential diagnosis in this patient.

1. Persistent pulmonary hypertension of the neonate. This is likely, given the severity and persistence of the very abnormal alveolar to arterial oxygen gradient ($AaDo_2$). Pulmonary hypertension may be associated with MAS. It is important to consider that right-to-left shunting can occur associated with disorders such as myocardial dysfunction, sepsis, metabolic abnormalities, and others.

2. MAS. MAS with intrapulmonary (ventilation–perfusion mismatch) or extrapulmonary shunting (atrial or ductal shunting with pulmonary hypertension) may lead to desaturation despite high oxygen supplementation.
3. Pneumothorax. Infants with MAS are at high risk for pneumothorax. A pneumothorax can cause severe desaturation.
4. Gas trapping. Because this infant has a large tidal volume for the given pressure gradient (PIP − PEEP) and thus high compliance, a long-time constant of the respiratory system leading to gas trapping at a borderline high ventilator rate should be considered.
5. Other causes. There are other less frequent causes in the differential diagnosis.

■ **Diagnostic Tests.** The chest radiograph was obtained, repeat blood gases were followed, and pre- and postductal pulse oximetry and transcutaneous measurements of gases were monitored continuously. In addition, a complete blood count (CBC) and blood culture were obtained. Four extremity blood pressures and an echocardiogram were obtained.

■ **Working Diagnosis.** The chest radiograph showed bilateral gas trapping. The CBC and the blood cultures were negative. The echocardiogram was consistent with persistent pulmonary hypertension.

■ **Development of Management Plan.** The infant was given surfactant, and initial improvement was seen. However, during the next 24 hours, there were episodes of repeated intracardiac and ductal shunting, which led to the initiation of nitric oxide.

■ **Implementation and Evaluation of Effectiveness.** Nitric oxide resulted in a marked reduction in the shunting episodes. The infant was gradually weaned off FiO_2 and subsequently weaned off nitric oxide before extubation. He was entirely weaned off the ventilator and FiO_2 over the subsequent 3 days.

EVIDENCE-BASED PRACTICE BOX

RDS is the most common cause of respiratory distress in preterm neonates (Hamvas, 2011). Most children that are born extremely premature develop RDS in the first hours after birth. The incidence of RDS is progressively more common the lower the infant's gestational age. Up to 98% of infants born at 23 weeks and 86% of infants born at 28 weeks develop RDS (Stoll et al., 2010). Many of these are treated with surfactant (Stoll et al., 2010). RDS can develop in term infants born to mothers with diabetes or in term infants who have experienced asphyxia, but it is substantially less frequent than in premature infants.

Antenatal steroids accelerate lung maturation (Roberts, Brown, Medley, & Dalziel, 2017). Present recommendations are to give steroids to all mothers between 23 and 34 weeks gestational age with threatened delivery. Antenatal steroids significantly reduce the incidence of RDS in premature infants. Antenatal steroids also decrease mortality, intraventricular hemorrhage, necrotizing enterocolitis, and neurodevelopmental impairment (Carlo et al., 2011; Schmidt et al., 2006). Adverse effects have not been reported with the usual single course of antenatal steroids (Carlo et al., 2011; Schmidt et al., 2006). Data at the limits of viability (i.e., <25 weeks) show benefits to giving steroids to infants as early as 22 weeks with a reduction in mortality at all gestational ages between 23 and 27 weeks (Carlo et al., 2011; Travers et al., 2018).

The hallmark of RDS is deficiency of pulmonary surfactant. Surfactant reduces the alveolar surface tension, thus preventing alveolar collapse. Therapy is directed toward improving oxygenation as well as maintaining optimal lung volume. CPAP can be used to prevent volume loss during expiration. Exogenous surfactants are also quite effective at treating RDS but require endotracheal intubation and exposure to mechanical ventilation. Early clinical trials indicated that prophylactic surfactant administration to extremely premature infants in the delivery room is more effective than waiting for the treatment after development of RDS (Soll & Morley, 2001). However, more recent trials show equivalence between prophylactic surfactant administration and early CPAP with rescue surfactant. However, the recent randomized clinical trials (Dunn et al., 2011; Finer et al., 2010) and the Cochrane review (Rojas-Reyes et al., 2012) indicate that early CPAP with selective surfactant for infants who require intubation reduces death/BPD when compared with prophylactic surfactant administration in extremely preterm infants.

References

Carlo, W. A., McDonald, S. A., Fanaroff, A. A., Vohr, B. R., Stoll, B. J., Ehrenkranz, R. A., . . . Higgins, R. D. (2011). Association of antenatal corticosteroids with mortality and neurodevelopmental outcomes among infants born at 22 to 25 weeks' gestation. *Journal of the American Medical Association, 306*, 2348–2358. doi:10.1001/jama.2011.1752

Dunn, M. S., Kaempf, J., de Klerk, A., de Klerk, R., Reilly, M., Howard, D., . . . Soll, R. F. (2011). Randomized trial comparing 3 approaches to the initial respiratory management of preterm neonates. *Pediatrics, 128*(5), e1069–e1076. doi:10.1542/peds.2010-3848

Finer, N. N., Carlo, W. A., Walsh, M. C., Rich, W., Gantz, M. G., Laptook, A. R., . . . Higgins, R. D. (2010, May 27). Early CPAP versus surfactant in extremely preterm infants. *New England Journal of Medicine, 362*(21), 1970–1979. doi:10.1056/NEJMoa0911783

Hamvas, A. (2011). The respiratory system: Part 3 pathophysiology and management of respiratory distress syndrome. In A. A. Fanaroff, R. J. Martin, & M. C. Walsh (Eds.), *Fanaroff & Martin's neonatal-perinatal medicine: Diseases of the fetus and infant* (9th ed., pp. 1106–1115). St Louis, MO: Mosby.

Roberts, D., Brown, J., Medley, N., & Dalziel, S. R. (2017). Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database of Systematic Reviews*, (3), CD004454.

Rojas-Reyes, M. X., Morley, C. J., & Soll, R. (2012). Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. *Cochrane Database of Systematic Reviews*, (3), CD000510. doi:10.1002/14651858.CD000510.pub2

Schmidt, B., Roberts, R. S., Davis, P., Doyle, L. W., Barrington, K. J., Ohlsson, A., . . . Tin, W. (2006). Caffeine therapy for apnea of prematurity. *New England Journal of Medicine, 354*(20), 2179–2180. doi:10.1056/NEJMoa054065

Soll, R. F., & Morley, C. J. (2001). Prophylactic versus selective use of surfactant for preventing morbidity and mortality in preterm infants. *Cochrane Database of Systematic Reviews*, (2), CD000510. doi:10.1002/14651858.CD000510

Stoll, B. J., Hansen, N. I., Bell, E. F., Shankaran, S., Laptook, A. R., Walsh, M. C., . . . Higgins, R. D. (2010). Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. *Pediatrics, 126*, 443–456. doi:10.1542/peds.2009-2959

Travers, C. P., Carlo, W. A., McDonald, S. A., Das, A., Bell, E. F., Ambalavanan, N., . . . & Shankaran, S. (2018). Mortality and pulmonary outcomes of extremely preterm infants exposed to antenatal corticosteroids. *American Journal of Obstetrics and Gynecology, 218*(1), e131–130 e113.

PARENT VOICES

Heather McKinnis

Our micro-preemie was a complete surprise. My perfect pregnancy ended abruptly after just 4 hours of labor. I was given one steroid injection as they rapidly prepped me for my emergency C-section. Owen came into the world with low APGAR scores that did slightly improve as the NICU team worked on him. He was stabilized and moved to the NICU. When I first saw him, 12 hours later, he was so tiny and hooked up to so many pieces of equipment, including a vent that we would get to know well over the next week. Miraculously, my little fighter only required intubation for 8 days. He spent another week on CPAP and several weeks on high flow cannula. We had prepared to take him home with oxygen support but a week and a half before discharge, he proved us all wrong and came off oxygen as well. Throughout this entire journey, I was incredibly grateful for the patience and kindness of our nurses. They took the time to explain everything to me, helped me wrap my mind around the fragility of my baby, and how I could best help him thrive.

Laurel Kapferer, MS

Our son Blake was born via a scheduled C-section at 37 weeks. When he was born, everything appeared to be fine. He weighed 7 lbs 1.4 oz, and was breathing on his own. He was placed on my chest as soon as we left the operating room and began breastfeeding almost immediately. When he was 2 hours old, he went for a routine examination at which time everything quickly changed. During his examination, Blake went into respiratory distress and was rushed to the NICU.

The doctors told us that his respiratory distress was due to his lungs not being completely matured, the presence of fluid in his lungs, or both. Blake was hooked up to monitors and oxygen, which made holding him difficult. Anytime it was loud or Blake got excited, his oxygen saturation would drop, and eventually he had to be intubated and given two rounds of surfactant. Seeing Blake with tubes down his throat was absolutely excruciating for us. Even though we had been in the NICU before, nothing could have prepared us for that. Fortunately, the surfactant worked and all tubes and oxygen were removed. Blake was able to maintain his O_2 sats on room air. When he was 6 days old, he was discharged from the NICU. Today Blake is a happy, healthy 5-year-old. The only complication that he has from his NICU stay are fractures in the base of his baby teeth from being intubated.

Blake's journey was made more difficult because we knew the pain of losing a child. His brother had passed away the year prior while in the NICU. We were so very fortunate to have such amazing NICU doctors and nurses caring for Blake. They all knew our story and they all did everything they could to help us through. They went above and beyond and really understood the trauma and posttraumatic stress disorder (PTSD) that we suffered. They took the time to look at the details of our past and made sure to put us in a different room from our previous NICU stay. They made sure not to discharge us on the same count of days that our other child passed on. They also met with us every day and told us what would likely happen so that we were emotionally prepared.

The compassion and understanding that our NICU team showed us made such an incredible impact on our journey and we are eternally grateful for them.

Jennifer M. Driscoll

Our daughter, Lilian Hope, was born 7 weeks premature, weighing only 2 lbs 12 oz and 15 inches long. Lily's lungs were her main problem, as they are for many preemies, because the lungs are the last thing to develop. On the day she was born, she was doing well, but still needed a CPAP machine to help her breathe. As the day progressed, her condition worsened. She was given nitric oxide, put onto a ventilator to breathe for her, and needed an oscillator to vibrate the lungs to help the flow of oxygen. Due to the force of the ventilator and oscillator, an air sac in her lungs burst and she had a chest tube inserted. Additionally, she had an erratic blood pressure, jaundice, and needed multiple blood transfusions. But the miracle continued as she began to gain strength inside herself; she came off the oscillator after 7 days and took out the ventilator herself. By day 8 we were able to hold her for the first time. She ended up by only needing to stay in the NICU at Lehigh Valley Hospital for 24 days and was able to come home at a mere 3 lbs 11 oz.

Our son, Aidan Patrick, was also born only 4 weeks premature, weighing 4 lbs 11 oz and 18 inches long. These few weeks, pounds, and inches may seem small but were huge victories for us. I was labeled high risk as soon as I found out I was pregnant and put on aspirin and bed rest much sooner because we knew what happened when Lily was born. Aidan's NICU stay was much shorter than Lily's, only a few days. Unfortunately, because of that, Aidan didn't qualify for the RSV vaccine as Lily did, and by 4 months old he was hospitalized on oxygen for over a week with RSV.

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This incident catapulted his asthma and subsequent allergy issues. Aidan has been hospitalized seven times since that RSV diagnosis with severe asthma flare-ups. Allergies and sickness trigger his asthma, so he is on two maintenance inhalers and daily medication and continues to see pediatric pulmonologists and allergists for his lung issues.

Both Aidan and Lily were born early because I had preeclampsia. They both had a very rough beginning, but with their strength, wonderful doctors and nurses, hope, and prayers, they have been able to rise above it all.

Keira Sorrells

One of my daughters spent 14 months on the ventilator and had severe reflux, causing her to have extreme oral aversions and tracheomalacia. We spent the first 60 days of her 291-day NICU stay simply staring at her because we were told she was too fragile to hold. As a parent, this was absolutely devastating. NICU parents confront so many barriers in access to their children, from the locked door we have to be buzzed through to gain entry to the yellow gowns we wear over our clothing and of course the isolette, tubes, and wires encasing our babies. Parents of typical, healthy newborns obtain instantaneous and open access to their babies at birth while we are stripped of every maternal instinct we have. I wish, during those 60 days, something could have been done to allow us to be closer to her. If there was any chance of holding her before she was 2 months old we would have cherished every minute. We spent so many hours simply sitting next to her and watching the hours pass by, hoping and praying she would be strong enough to hold.

ONLINE RESOURCES

Association of Women's Health, Obstetric and Neonatal Nurses. Retrieved from http://www.awhonn.org

National Association of Neonatal Nurses. Retrieved from http://www.nann.org

National Institutes of Health. (n.d.). *NICHD Neonatal Research Network (NRN): Extremely preterm birth outcome data*. Retrieved from https://www1.nichd.nih.gov/epbo-calculator/Pages/epbo_case.aspx

Neonatology on the web. Retrieved from http://www.neonatology.org

NICHD calculators (NICHD gestational age calculator; mortality calculator; survival calculator; extreme prematurity calculator; neonatal outcomes calculator, preemie calculator). Retrieved from https://neonatal.rti.org/index.cfm?fuseaction=AdjustedAgeCalculator.main

The NICHD Cochrane Neonatal Collaborative. Retrieved from https://neonatal.cochrane.org/

REFERENCES

Alfaleh, K., Smyth, J. A., Roberts, R. S., Solimano, A., Asztalos, E. V., & Schmidt, B. (2008). Prevention and 18-month outcomes of serious pulmonary hemorrhage in extremely low birth weight infants: Results from the trial of indomethacin prophylaxis in preterms. *Pediatrics, 121*(2), e233–e238. doi:10.1542/peds.2007-0028

Als, H. (1998). Developmental care in the newborn intensive care unit. *Current Opinion in Pediatrics, 10*, 138–142. doi:10.1097/00008480-199804000-00004

Askie, L. M., Darlow, B. A., Davis, P. G., Finer, N., Stenson, B., Vento, M., & Whyte, R. (2017). Effects of targeting lower versus higher arterial oxygen saturations on death or disability in preterm infants. *Cochrane Database of Systematic Reviews*, (4), CD011190. doi:10.1002/14651858.CD011190.pub2

Askie, L. M., Darlow, B. A., Finer, N., Schmidt, B., Stenson, B., Tarnow-Mordi, W., . . . Simes, R. J. (2018). Association between oxygen saturation targeting and death or disability in extremely preterm infants in the Neonatal Oxygenation Prospective Meta-Analysis Collaboration. *Journal of the American Medical Association, 319*(21), 2190–2201. doi:10.1001/jama.2018.5725

Aziz, A., & Ohlsson, A. (2012). Surfactant for pulmonary haemorrhage in neonates. *Cochrane Database of Systematic Reviews*, (7), CD005254. doi:10.1002/14651858.CD005254.pub3

Battista, M. A., & Carlo, W. A. (1992). Differential diagnosis of acute respiratory distress in the neonate. *Tufts University School of Medicine and Floating Hospital for Children Reports on Neonatal Respiratory Diseases, 2*(3), 1–4, 9–11.

Carlo, W. A., & Di Fiore, J. M. (2011). The respiratory system: Part 2 assessment of pulmonary function. In R. J. Martin, A. A. Fanaroff & M. C. Walsh (Eds.), *Fanaroff and Martin's neonatal-perinatal medicine: Diseases of the fetus and infant* (9th ed., 1092–1105). St Louis, MO: Mosby.

Carlo, W. A., Finer, N. N., Walsh, M. C., Rich, W., Gantz, M. G., Laptook, A. R., . . . Higgins, R. D. (2010). Target ranges of oxygen saturation in extremely preterm infants. *New England Journal of Medicine, 362*, 1959–1969. doi:10.1056/NEJMoa0911781

Carlo, W. A., McDonald, S. A., Fanaroff, A. A., Vohr, B. R., Stoll, B. J., Ehrenkranz, R. A., . . . Higgins, R. D. (2011). Association of antenatal corticosteroids with mortality and neurodevelopmental outcomes among infants born at 22 to 25 weeks' gestation. *Journal of the American Medical Association, 306*, 2348–2358. doi:10.1001/jama.2011.1752

Cedin, A. C., Atallah, A. N., Andriolo, R. B., Cruz, O. L., & Pignatari, S. N. (2012). Surgery for congenital choanal atresia. *Cochrane Database of Systematic Reviews*, (2), CD008993. doi:10.1002/14651858.CD008993.pub2

Chettri, S., Adhisivam, B., & Bhat, B. V. (2015). Endotracheal suction for nonvigorous neonates born through meconium stained amniotic fluid: A randomized controlled trial. *Journal of Pediatrics, 166*(5), 1208–1213.e1. doi:10.1016/j.jpeds.2014.12.076

Colby, C. E., Lally, K. P., Hintz, S. R., Lally, P. A., Tibboel, D., Moya, F. R., & VanMeurs, K. P. (2004). Surfactant replacement therapy on ECMO does not improve outcome in neonates with congenital diaphragmatic hernia. *Journal of Pediatric Surgery, 39*, 1632–1637. doi:10.1016/j.jpedsurg.2004.07.005

Committee on Obstetric Practice. (2017). Committee opinion no. 712: Intrapartum management of intraamniotic infection. *Obstetrics and Gynecology, 130*(2), e95–e101. doi:10.1097/AOG.0000000000002236

Cools, F., Offringa, M., & Askie, L. M. (2015). Elective high frequency oscillatory ventilation versus conventional ventilation for acute pulmonary dysfunction in preterm infants. *Cochrane Database*

of Systematic Reviews, (3), CD000104. doi:10.1002/14651858.CD000104.pub4

Cordero, L., Sananes, M., & Ayers, L. W. (2000). Comparison of a closed (Trach Care MAC) with an open endotracheal suction system in small premature infants. *Journal of Perinatology, 20*, 151–156. doi:10.1038/sj.jp.7200330

Darlow, B. A., & Graham, P. J. (2011). Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birthweight infants. *Cochrane Database of Systematic Reviews*, (10), CD000501. doi:10.1002/14651858.CD000501.pub3

Davidson, D., Barefield, E. S., Kattwinkel, J., Dudell, G., Damask, M., Straube, R., . . . Chang, C. T. (1998). Inhaled nitric oxide for the early treatment of persistent pulmonary hypertension of the term newborn: A randomized, double-masked, placebo-controlled, dose-response multicenter study. *Pediatrics, 101*, 325–334. doi:10.1542/peds.101.3.325

De Jesus, L. C., Sood, B. G., Shankaran, S., Kendrick, D., Das, A., Bell, E. F., . . . Higgins, R. D. (2015). Antenatal magnesium sulfate exposure and acute cardiorespiratory events in preterm infants. *American Journal of Obstetrics and Gynecology, 212*(1), 94.e91–94.e97. doi:10.1016/j.ajog.2014.07.023

Dhillon, R. (2011, January 30). The management of neonatal pulmonary hypertension. *Archives of Disease in Childhood:Fetal and Neonatal Edition, 97*(3), F223–F228. doi:10.1136/adc.2009.180091

Doyle, L. W., Cheong, J. L., Ehrenkranz, R. A., & Halliday, H. L. (2017a). Early (< 8 days) systemic postnatal corticosteroids for prevention of bronchopulmonary dysplasia in preterm infants. *Cochrane Database of Systematic Reviews*, (10), CD001146. doi:10.1002/14651858.CD001146.pub5

Doyle, L. W., Cheong, J. L., Ehrenkranz, R. A., & Halliday, H. L. (2017b). Late (> 7 days) systemic postnatal corticosteroids for prevention of bronchopulmonary dysplasia in preterm infants. *Cochrane Database of Systematic Reviews*, (10), CD001145. doi:10.1002/14651858.CD001145.pub4

Dunn, M. S., Kaempf, J., de Klerk, A., de Klerk, R., Reilly, M., Howard, D., . . . Soll, R. F. (2011). Randomized trial comparing 3 approaches to the initial respiratory management of preterm neonates. *Pediatrics, 128*(5), e1069–e1076. doi:10.1542/peds.2010-3848

Ehrenkranz, R. A., Walsh, M. C., Vohr, B. R., Jobe, A. H., Wright, L. L., Fanaroff, A. A., . . . Poole K (2005). Validation of the National Institutes of Health consensus definition of bronchopulmonary dysplasia. *Pediatrics, 116*, 1353–1360. doi:10.1542/peds.2005-0249

El Shahed, A. I., Dargaville, P., Ohlsson, A., & Soll, R. F. (2007). Surfactant for meconium aspiration syndrome in full term/near term infants. *Cochrane Database of Systematic Reviews*, (3), CD002054. doi:10.1002/14651858.CD002054.pub2

Finer, N. N., & Barrington, K. J. (2006). Nitric oxide for respiratory failure in infants born at or near term. *Cochrane Database of Systematic Reviews*, (4), CD000399. doi:10.1002/14651858.CD000399.pub2

Finer, N. N., Carlo, W. A., Walsh, M. C., Rich, W., Gantz, M. G., Laptook, A. R., . . . Higgins, R. D. (2010, May 27). Early CPAP versus surfactant in extremely preterm infants. *New England Journal of Medicine, 362*(21), 1970–1979. doi:10.1056/NEJMoa0911783

Gentle, S. J., Travers, C. P., & Carlo, W. A. (2018). Caffeine controversies. *Current Opinion in Pediatrics, 30*(2), 177–181. doi:10.1097/MOP.0000000000000588

Gray, P. H., Flenady, V. J., Charles, B. G., & Steer, P. A. (2011). Caffeine citrate for very preterm infants: Effects on development, temperament and behaviour. *Journal of Paediatrics and Child Health, 47*(4), 167–172. doi:10.1111/j.1440-1754.2010.01943.x

Greenough, A., & Milner, A. D. (2005). Pulmonary disease of the newborn. In J. M. Rennie (Ed.), *Roberton's textbook of neonatology* (4th ed., pp. 468–553). London, England: Churchill Livingstone.

Greenough, A., Murthy, V., Milner, A. D., Rossor, T. E., & Sundaresan, A. (2016). Synchronized mechanical ventilation for respiratory support in newborn infants. *Cochrane Database of Systematic Reviews*, (9), CD000456. doi:10.1002/14651858.CD000456.pub4

Gyamfi-Bannerman, C., Thom, E. A., Blackwell, S. C., Tita, A. T., Reddy, U. M., Saade, G. R., . . . Jain, L. (2016). Antenatal betamethasone for women at risk for late preterm delivery. *New England Journal of Medicine, 374*(14), 1311–1320. doi:10.1056/NEJMoa1516783

Hamvas, A. (2011). The respiratory system: Part 3 pathophysiology and management of respiratory distress syndrome. In A. A. Fanaroff, R. J. Martin, & M. C. Walsh (Eds.), *Fanaroff & Martin's neonatal-perinatal medicine: Diseases of the fetus and infant* (9th ed., pp. 1106–1115). St Louis, MO: Mosby.

Hornik, C. P., Benjamin, D. K., Becker, K. C., Benjamin, D. K., Jr., Li, J., Clark, R. H., . . . Smith, P. B. (2012). Use of the complete blood cell count in early-onset neonatal sepsis. *The Pediatric Infectious Disease Journal, 31*(8), 799–802. doi:10.1097/INF.0b013e318256905c

Janér, C., Pitkänen, O. M., Helve, O., & Andersson, S. (2011, July 18). Airway expression of the epithelial sodium channel α-subunit correlates with cortisol in term newborns. *Pediatrics, 128*, e414. doi:10.1542/peds.2011-0167

Jobe, A. H., & Bancalari, E. (2001). Bronchopulmonary dysplasia. *American Journal of Respiratory Critical Care Medicine, 163*, 1723–1729. doi:10.1164/ajrccm.163.7.2011060

Johnson, L. H., Mapp, D. C., Rouse, D. J., Spong, C. Y., Mercer, B. M., Leveno, K. J., . . . Caritis, S. N. (2012). Association of cord blood magnesium concentration and neonatal resuscitation. *Journal of Pediatrics, 160*(4), 573–577.e1. doi:10.1016/j.jpeds.2011.09.016

Kelleher, J., Bhat, R., Salas, A. A., Addis, D., Mills, E. C., Mallick, H., . . . Carlo, W. A. (2013). Oronasopharyngeal suction versus wiping of the mouth and nose at birth: A randomised equivalency trial. *Lancet, 382*(9889), 326–330. doi:10.1016/S0140-6736(13)60775-8

Khansa, I., Hall, C., Madhoun, L. L., Splaingard, M., Baylis, A., Kirschner, R. E., & Pearson, G. D. (2017). Airway and feeding outcomes of mandibular distraction, tongue-lip adhesion, and conservative management in Pierre Robin sequence: A prospective study. *Plastic and Reconstructive Surgery, 139*(4), 975e–983e. doi:10.1097/PRS.0000000000003167

Litmanovitz, I., & Carlo, W. A. (2008). Expectant management of pneumothorax in ventilated neonates. *Pediatrics, 122*, e975–e979. doi:10.1542/peds.2008-1269

Malviya, S., Reynolds, P. I., Voepel-Lewis, T., Siewert, M., Watson, D., Tait, A. R., & Tremper, K. (2000). False alarms and sensitivity of conventional pulse oximetry versus the Masimo SET technology in the pediatric post anesthesia care unit. *Anesthesia and Analgesia, 90*(6), 1336–1340. doi:10.1097/00000539-200006000-00013

Mok, Q., Yates, R., & Tasker, R. C. (1999). Persistent pulmonary hypertension of the term neonate: A strategy for management. *European Journal of Pediatrics, 158*, 825–827. doi:10.1007/s004310051214

Morley, C. J., Davis, P. G., Doyle, L. W., Brion, L. P., Hascoet, J. M., & Carlin, J. B. (2008). Nasal CPAP or intubation at birth for very preterm infants. *New England Journal of Medicine, 358*(7), 700–708. doi:10.1056/NEJMoa072788

Nangia, S., Sunder, S., Biswas, R., & Saili, A. (2016). Endotracheal suction in term non vigorous meconium stained neonates-A pilot study. *Resuscitation, 105*, 79–84. doi:10.1016/j.resuscitation.2016.05.015

The Neonatal Inhaled Nitric Oxide Study Group. (1997). Inhaled nitric oxide in full-term and nearly full-term infants with hypoxic respiratory failure. *New England Journal of Medicine, 336*(9), 597–604. doi:10.1056/NEJM199702273360901

O'Donnell, C. P., Kamlin, C. O., Davis, P. G., Carlin, J. B., & Morley, C. J. (2007). Clinical assessment of infant colour at delivery. *Archives of Disease in Childhood. Fetal and Neonatal Edition, 92*(6), F465–F467. doi:10.1136/adc.2007.120634

Roberts, D., Brown, J., Medley, N., & Dalziel, S. R. (2017). Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database of Systematic Reviews*, (3), CD004454.

Rojas-Reyes, M. X., Morley, C. J., & Soll, R. (2012). Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. *Cochrane Database of Systematic Reviews*, (3), CD000510. doi:10.1002/14651858.CD000510.pub2

Schmidt, B., Roberts, R. S., Davis, P., Doyle, L. W., Barrington, K. J., Ohlsson, A., . . . Tin, W. (2006). Caffeine therapy for apnea of

prematurity. *New England Journal of Medicine, 354*(20), 2179–2180. doi:10.1056/NEJMoa054065

Schmidt, B., Whyte, R. K., Asztalos, E. V., Moddemann, D., Poets, C., Rabi, Y., . . . Roberts, R. S. (2013). Effects of targeting higher vs lower arterial oxygen saturations on death or disability in extremely preterm infants: A randomized clinical trial. *Journal of the American Medical Association, 309*(20), 2111–2120. doi:10.1001/jama.2013.5555

Soll, R. F., & Morley, C. J. (2001). Prophylactic versus selective use of surfactant for preventing morbidity and mortality in preterm infants. *Cochrane Database of Systematic Reviews*, (2), CD000510. doi:10.1002/14651858.CD000510

Stenson, B., Brocklehurst, P., & Tarnow-Mordi, W. (2011). Increased 36-week survival with high oxygen saturation target in extremely preterm infants. *New England Journal of Medicine, 364*, 1680–1682. doi:10.1056/NEJMc1101319

Stenson, B. J., Tarnow-Mordi, W. O., Darlow, B. A., Simes, J., Juszczak, E., Askie, L., . . . Brocklehurst, P. (2013). Oxygen saturation and outcomes in preterm infants. *New England Journal of Medicine, 368*(22), 2094–2104. doi:10.1056/NEJMoa1302298

Stoll, B. J., Hansen, N. I., Bell, E. F., Shankaran, S., Laptook, A. R., Walsh, M. C., . . . Higgins, R. D. (2010). Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. *Pediatrics, 126*, 443–456. doi:10.1542/peds.2009-2959

Stroustrup, A., Trasande, L., & Holzman, I. R. (2012). Randomized controlled trial of restrictive fluid management in transient tachypnea of the newborn. *Journal of Pediatrics, 160*(1), 38–43.e31. doi:10.1016/j.jpeds.2011.06.027

SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network, Finer, N. N., Carlo, W. A., Walsh, M. C., Rich, W., Gantz, M. G., … Higgins, R. D. (2010). Early CPAP versus surfactant in extremely preterm infants. *The New England Journal of Medicine, 362*(21),1970–1979. doi:10.1056/NEJMoa0911783. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/20472939

Thome, U. H., Carlo, W. A., & Pohlandt, F. (2005). Ventilation strategies and outcome in randomized trials of high frequency ventilation. *Archives of Disease in Childhood: Fetal and Neonatal Edition, 90*, F466–F473. doi:10.1136/adc.2004.068437

Tita, A. T., Landon, M. B., Spong, C. Y., Lai, Y., Leveno, K. J., Varner, M. W., . . . Mercer, B. M. (2009). Timing of elective repeat cesarean delivery at term and neonatal outcomes. *New England Journal of Medicine, 360*(2), 111–120. doi:10.1056/NEJMoa0803267

Travers, C. P., Carlo, W. A., McDonald, S. A., Das, A., Bell, E. F., Ambalavanan, N., . . . Higgins, R. D. (2018). Mortality and pulmonary outcomes of extremely preterm infants exposed to antenatal corticosteroids. *American Journal of Obstetrics and Gynecology, 218*(1), 130.e1–130.3. doi:10.1016/j.ajog.2017.11.554

UK Collaborative ECMO Trial Group. (1996). UK collaborative randomised trial of neonatal extracorporeal membrane oxygenation. *Lancet, 348*(9020), 75–82. doi:10.1016/S0140-6736(96)04100-1

Vain, N. E., Szyld, E. G., Prudent, L. M., Wiswell, T. E., Aguilar, A. M., & Vivas, N. I. (2004). Oropharyngeal and nasopharyngeal suctioning of meconium-stained neonates before delivery of their shoulders: Multicentre, randomised controlled trial. *Lancet, 364*, 597–602. doi:10.1016/S0140-6736(04)16852-9

Walsh-Sukys, M. C., Tyson, J. E., Wright, L. L., Bauer, C. R., Korones, S. B., Stevenson, D. K., . . . Fanaroff, A. A. (2000). Persistent pulmonary hypertension of the newborn in the era before nitric oxide: Practice variation and outcomes. *Pediatrics, 105*, 14–20. doi:10.1542/peds.105.1.14

Wyckoff, M. H., Aziz, K., Escobedo, M. B., Kapadia, V. S., Kattwinkel, J., Perlman, J. M., . . . Zaichkin, J. G. (2015). Part 13: Neonatal resuscitation: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care (Reprint). *Pediatrics, 136*(Suppl. 2), S196–S218. doi:10.1542/peds.2015-3373G

Yin, R., Zhang, R., Wang, J., Yuan, L., Hu, L., Jiang, S., . . . Cao, Y. (2017). Effects of somatostatin/octreotide treatment in neonates with congenital chylothorax. *Medicine, 96*(29), e7594. doi:10.1097/MD.0000000000007594

Zaichkin, J., & Weiner, G. M. (2011, February). Neonatal Resuscitation Program (NRP) 2011: New science, new strategies. *Advances in Neonatal Care, 11*(1), 43–51. doi:10.1097/ANC.0b013e31820e429f

Zalla, J. M., Stoddard, G. J., & Yoder, B. A. (2015). Improved mortality rate for congenital diaphragmatic hernia in the modern era of management: 15 year experience in a single institution. *Journal of Pediatric Surgery, 50*(4), 524–527. doi:10.1016/j.jpedsurg.2014.11.002

CHAPTER 7

Cardiovascular System

Donna A. Goff

INTRODUCTION

This chapter presents the physiology of normal cardiac function, including fetal circulatory patterns and the changes that occur during transition to extrauterine life. The most common congenital heart defects (CHDs) and cardiac complications are described including information about the incidence, hemodynamics, manifestations, diagnosis, and medical and surgical management. The importance of prenatal detection of CHD and critical congenital heart defect (CCHD) pulse oximetry screening is discussed. Risk factors for brain injury in the neonate with CHD and age-related neurodevelopmental (ND) problems are reviewed. The chapter concludes with a discussion about the support of the family of an infant with a CHD. A case study is used to illustrate the complex care required by infants and families of infants with cardiac disorders.

CARDIOVASCULAR ADAPTATION

Fetal Circulation

Knowledge of the normal route of fetal blood flow is essential to understand the circulatory changes that occur in the newborn at delivery. The pattern of fetal circulation is illustrated in Figure 7.1. Fetal circulation involves four unique anatomic features.

In fetal life, the placenta serves as the exchange organ for oxygen and carbon dioxide and for nutrients and wastes. Fetal circulation involves parallel circulation, which is different from series circulation—right ventricle (RV) pumps deoxygenated blood to the lungs, which return oxygenated blood to the left ventricle (LV), which pumps blood to the body—seen postnatally. The oxygenated blood from the placenta enters the umbilical vein (UV), and the ductus venosus (DV) allows approximately one third of this oxygenated blood to bypass the liver to stream right to left across the foramen ovale (FO), an opening in the atrial septum. This oxygenated blood enters the LV, which then pumps the well-oxygenated blood to the developing brain. Deoxygenated blood from the superior vena cava (SVC) and inferior vena cava (IVC) enters the right atrium (RA) to the RV, which pumps the blood into the main pulmonary artery. Since the lungs are collapsed in utero, only 5% to 10% of the blood flow in the

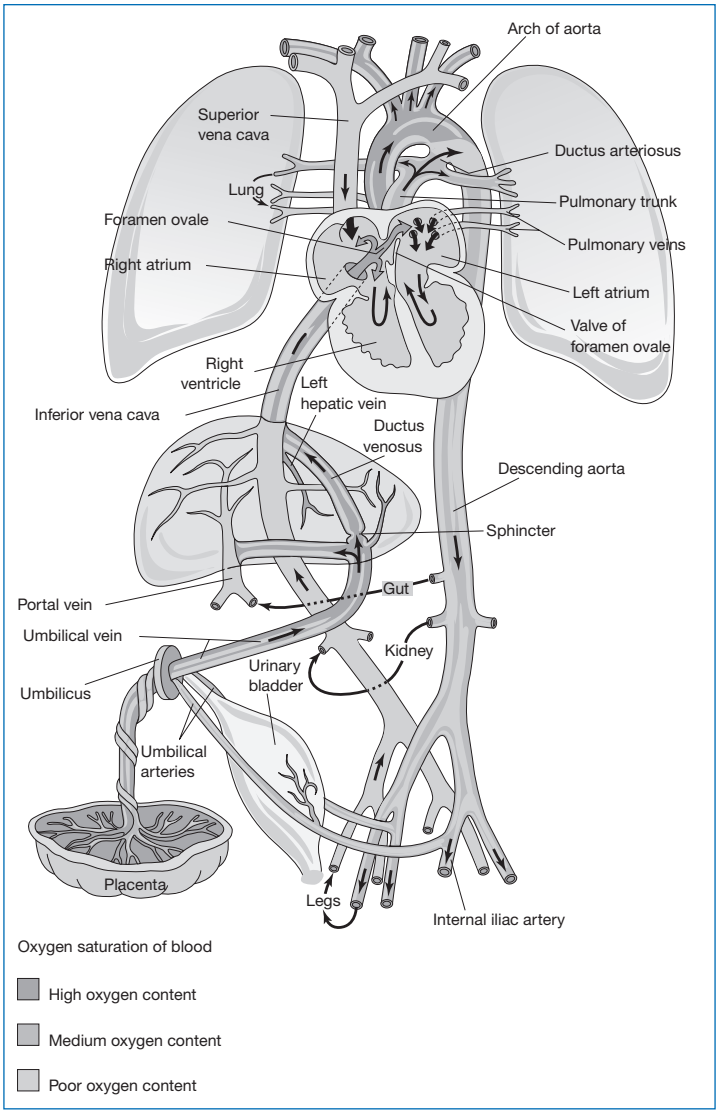

FIGURE 7.1 Anatomical features and pattern of fetal circulation.

Source: Adapted and modified from Ross Laboratories, Columbus, OH, Clinical Education Aid, 1985.

pulmonary artery perfuses the lungs, so the majority of the blood flow shunts across the ductus arteriosus (DA) into the descending aorta and returns to the placenta via the umbilical artery (UA; Godfrey & Rychik, 2012; Park, 2014; Rudolph, 2001; Webb, Smallhorn, Therrien, & Redington, 2012).

Extrauterine Circulation

The cardiac and pulmonary systems undergo drastic changes at birth; these changes usually occur immediately upon onset of respiration. The most significant change is that the lungs now assume the role of primary oxygenator. Clamping of the umbilical cord removes the placenta, and subsequently results in immediate circulatory changes in the newborn. With the first breath and occlusion of the umbilical cord, the newborn's systemic vascular resistance is elevated, decreasing the amount of blood flow through the DA. Cord occlusion causes an increase in blood pressure and a corresponding stimulation of the aortic baroreceptors and the sympathetic nervous system. The onset of respiration and consequent lung expansion causes a decrease in pulmonary vascular resistance secondary to the direct effect of oxygen and carbon dioxide on the blood vessels. Pulmonary vascular resistance decreases as arterial oxygen content increases and arterial carbon dioxide decreases (Park, 2014; Webb et al., 2012).

Most of the RV output flows through the lungs and increases the pulmonary venous return to the left atrium (LA). This increased blood flow into the lungs that returns to the heart results in an increase in pressure in the LA, and, combined with the increased systemic vascular resistance, functionally closes the FO.

The DA functionally closes around 12 to 15 hours after birth as a result of constriction of the medial smooth muscle. The DA is anatomically constricted, becoming the ligamentum arteriosum by 3 weeks of age as a result of changes that occur in the endothelium and subintimal layers in response to oxygen, prostaglandin E_2 (PGE_2), acetylcholine, and bradykinin. Clamping of the umbilical cord causes the cessation of blood flow through the UV, DV, and UA (Park, 2014; Rudolph, 2001).

Functional closure refers to the cessation of flow through the structure caused by changes in pressure. *Anatomic closure* refers to obliteration of the structure by constriction as a result of intraluminal growth of tissue.

Because anatomic closure of the fetal pathways lags behind functional closure, the shunts may open and close intermittently before anatomic closure, resulting in transient functional murmurs.

Pulmonary artery pressure remains high for several hours after delivery. As the pulmonary vascular resistance decreases, the direction of blood flow through the DA changes. Initially, the PDA is bidirectional, the flow becomes entirely left to right typically by 24 to 48 hours of life, and the DA may be functionally insignificant by 48 hours of life. Intermittent or functional murmurs do not cause any cardiovascular compromise for the newborn and are not clinically significant. Conditions that cause transient opening of fetal shunts, allowing deoxygenated blood to shunt from the right side of the heart to the left, thereby bypassing the pulmonary circuit, produce transient cyanosis. Any murmur or cyanosis in the newborn should be carefully evaluated and monitored to detect cardiovascular abnormalities (Jones, 2005; Park, 2014; Webb et al., 2012). Hypoxemia and acidosis can cause a functionally constricted DA to reopen, while the pulmonary artery and arterioles respond by constricting (Park, 2014; Webb et al., 2012).

NORMAL CARDIAC FUNCTION

The normal anatomy of the heart is shown in Figure 7.2.

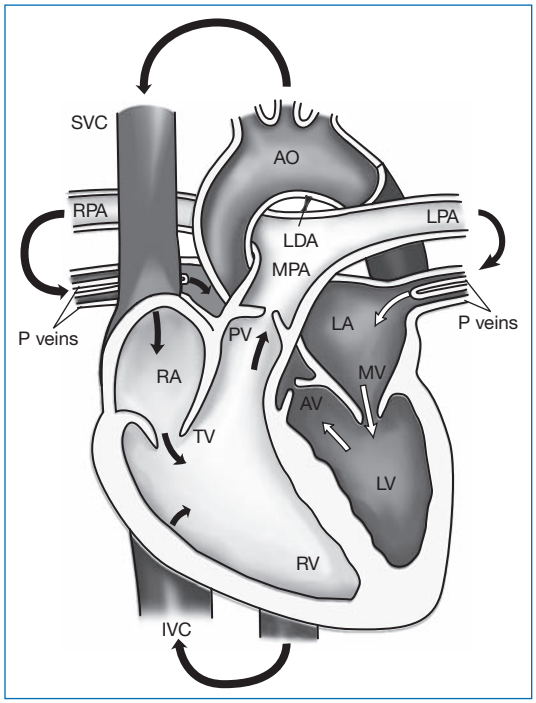

FIGURE 7.2 Normal cardiac anatomy and circulation.

AO, aorta; AV, aortic valve; IVC, inferior vena cava; LA, left atrium; LDA, ligamentum ductus arteriosus; LPA, left pulmonary artery; LV, left ventricle; MPA, main pulmonary artery; MV, mitral valve; PV, pulmonary valve; P veins, pulmonary veins; RA, right atrium; RPA, right pulmonary artery; RV, right ventricle; SVC, superior vena cava; TV, tricuspid valve.

Source: Adapted and modified from Ross Laboratories, Columbus, OH, Clinical Education Aid, 1985.

Cardiac Valves

Blood flow through the heart is directed through two sets of one-way valves. The atrioventricular valves (AVs) consist of the tricuspid valve and the mitral valve. The tricuspid valve connects the RA and the RV. The mitral valve connects the LA and the LV. The semilunar valves consist of the pulmonary valve and the aortic valve. The pulmonary valve connects the RV and the pulmonary artery. The aortic valve connects the LV and the aorta.

Cardiac Cycle

Normal cardiac function involves two stages: *systole* and *diastole*. During systole, contraction of the ventricle causes the pressure inside the ventricle to increase to approximately 70 mmHg in newborns (compared with 120 mmHg in adults). When sufficient pressure is generated, the aortic and pulmonary valves open and blood is ejected from the ventricles. As the blood flows from the ventricles, the pressure decreases, causing the aortic and pulmonary valves to close.

During diastole, the mitral and tricuspid valves open, and 70% of the blood in the atria enters the ventricles. A small portion of the aortic blood flows back into the coronary arteries to perfuse the heart. At the end of diastole, a small atrial contraction occurs (4–6 mmHg on the right side; 7–8 mmHg on the left side), and then the mitral and tricuspid valves close. Metabolism of the heart is decreased during diastole. The average newborn's cardiac cycle is approximately 0.4 second, with 0.2 second for diastole and 0.2 second for systole (based on a heart rate [HR] of approximately 150 beats per minute [bpm]; Opie & Hasenfuss, 2012).

Cardiac Output

Cardiac output (CO) is the amount of blood pumped by the LV in one minute. CO is equal to the stroke volume (SV) times the HR (CO = SV × HR). The SV is the volume of blood pumped per beat from each ventricle; the higher the SV, the greater the volume of blood in the systemic circulation. CO is influenced by changes in HR and pulmonary and systemic vascular resistance.

CO is influenced by the amount of blood returned to the heart, as explained by the Frank-Starling law, which states that within physiologic limits, the heart pumps all the blood that enters into it without allowing excessive accumulation of blood in the veins. The passive movement of blood through the veins, the thoracic pump, and the venous muscle pump determines venous return; normally, when increased volume enters the heart, contractility is increased as a response to stimulation of stretch receptors in the heart muscle. The newborn's heart has fewer muscle fibers and is unable to stretch sufficiently to accommodate increased volume; therefore, increased HR is the only effective mechanism by which the newborn can respond to increased volume (Mann, 2012; Opie & Hasenfuss, 2012).

Cardiac failure occurs when the volume exceeds the ability of the heart to pump. Local factors that affect venous return to the heart include hypoxia, acidosis, hypercarbia, hyperthermia, increased metabolic demand, and increased metabolites (potassium, adenosine triphosphate, and lactic acid).

Vascular pressure and resistance also influence CO. Pressure and resistance are inversely related: if pressure in the arterial bed is increased, resistance decreases and flow improves. The size (radius) of vessels influences resistance: the greater the radius of a vessel, the lower the resistance. Vessels obstructed by thrombosis or constriction have greater resistance to vascular flow (Mann, 2012; Opie & Hasenfuss, 2012).

Autonomic Cardiac Control

Cardiovascular function is modulated by the autonomic nervous system (ANS). Baroreceptors and chemoreceptors in the aorta and carotid sinus provide feedback to the ANS. Feedback from these receptors stimulates the parasympathetic or sympathetic nervous system. Most parasympathetic and sympathetic nervous system effects are on the atria, but decreased ventricular contractility may also occur.

The parasympathetic nervous system is less powerful than the sympathetic system. Stimulation of the parasympathetic nervous system results in vagal nerve stimulation and decreased HR. Right vagal stimulation affects the sinoatrial (SA) node, and left vagal stimulation affects the AV node. Acetylcholine is the active neurotransmitter for the preganglionic neurons of the parasympathetic and sympathetic nervous systems (Opie & Hasenfuss, 2012).

Stimulation of the sympathetic nervous system through the ganglionic chain releases norepinephrine and epinephrine, which act on the SA node, the AV node, the atria, and the ventricles. Maximal stimulation of the sympathetic nervous system can increase HR to 250 to 300 bpm. Contractility can be improved by approximately 100%. Alpha adrenergic and beta adrenergic receptors are stimulated. Alpha receptors cause increased contractility (inotropic) and increased rate (chronotropic); beta-2 receptors cause vasodilation, bronchodilation, and smooth muscle relaxation (Kaplan, 2011).

Term newborns have a decreased number of receptors but are capable of normal cardiovascular system function. The preterm newborn is not able to smoothly maintain autonomic function, and energy expenditure is increased. Hence, cardiovascular signs such as color changes and bradycardia may occur because of excessive demand for ANS function.

CARDIAC ASSESSMENT

In many regions of the United States, less than 50% of CHD is detected prenatally (Quartermain et al., 2015). Early recognition of signs and symptoms of CHD resulting in earlier CHD diagnosis and treatment can potentially result in improved outcomes (Eckersley, Sadler, Parry, Finucane, & Gentles, 2016). CCHD pulse oximetry screening typically performed around 24 hours of age may contribute to earlier CHD diagnosis before ductal closure with the resultant hemodynamic collapse. Careful newborn assessment is a crucial component of newborn care. Cardiac assessment includes history taking, physical assessment, and interpretation of diagnostic tests. Review of the maternal, fetal, and neonatal history and type of prenatal screening performed is helpful in the cardiac evaluation of the newborn. Box 7.1 lists maternal and fetal conditions that are considered higher risk for fetal cardiac conditions resulting in referrals for fetal echocardiograms (Donofrio et al., 2014). Table 7.1 lists heart defects commonly associated with maternal drug use and conditions.

Typically, these pregnant mothers are considered higher risk and are screened with detailed ultrasounds and fetal echocardiograms resulting in prenatal detection of cardiac conditions (Donofrio et al., 2014). Sometimes, pregnant mothers who are considered higher risk may not have received adequate prenatal ultrasound and fetal echocardiogram screening; therefore, their newborns will require screening after birth since they are at increased risk for cardiac conditions. In addition, the fetal effects of uncontrolled diabetes during pregnancy, especially during the third trimester, may go undetected and will result in a newborn who is large for gestational age, sometimes with associated hypertrophic cardiomyopathy.

Methods of Assessment

Assessment for evidence of a cardiac problem begins with a careful history, followed by a thorough physical examination. Family history of hereditary diseases, CHD, or rheumatic fever increases the risk for certain CHD lesions (Table 7.2).

The overall incidence of CHDs is approximately 1%, or 8 per 1,000 live births, excluding persistent PDA in preterm newborns. Maternal history of CHD, however, increases the risk of recurrence from 3% to 7% (Donofrio et al., 2014).

A neonatal history of cyanosis, tachypnea without pulmonary disease, sweating, poor feeding, and pulmonary edema, or, in older infants, poor feeding and failure to gain weight, is suggestive of CHD. Careful evaluation of the maternal, fetal, and neonatal history, in conjunction with a thorough physical assessment, helps identify infants for whom further diagnostic testing with echocardiogram is indicated.

Physical examination of the newborn with a suspected cardiac condition includes inspection, palpation, and auscultation (Park, 2014).

Inspection

Valuable information about the cardiovascular system of the newborn can be obtained by observation of the newborn's general appearance before examination. The following states of the newborn should be observed: sleeping or awake, alert or lethargic, anxious or relaxed. Respiratory effort, including signs of respiratory distress such as nasal flaring, expiratory grunting, stridor, retractions, or paradoxical respirations, should be noted. Tachypnea and tachycardia are early signs of LV dysfunction (Park, 2014).

Box 7.1

COMMON MATERNAL AND FETAL INDICATIONS FOR REFERRAL FOR FETAL ECHOCARDIOGRAM

Indications With the Highest Risk Profile (estimated >2% absolute risk for fetal cardiac disease)

- Maternal pregestational diabetes mellitus
- Diabetes mellitus diagnosed in the first trimester
- Maternal phenylketonuria (uncontrolled)
- Maternal autoantibodies (SSA/SSB+)
- Maternal medications (ACE inhibitors, retinoic acid, NSAIDs in third trimester)
- Maternal first-trimester rubella infection
- Maternal infection with suspicion of fetal myocarditis
- Assisted reproductive technology
- CHD in first-degree relative of fetus (maternal, paternal, or sibling)
- First- or second-degree relative with disorder with Mendelian inheritance with CHD association
- Fetal cardiac or extracardiac abnormality suspected on obstetric ultrasound
- Fetal karyotype abnormality
- Fetal tachycardia or bradycardia, or frequent or persistent irregular heart rhythm
- Fetal increased NT >95% (>3 mm)
- Monochorionic twinning
- Fetal hydrops or effusions

Indications With a Lower Risk Profile (estimated >1% but <2% absolute risk for fetal cardiac disease)

- Maternal medications (anticonvulsants, lithium, vitamin A, SSRIs (only paroxetine), NSAIDs in first or second trimester)
- CHD in second-degree relative of fetus
- Fetal abnormality of umbilical cord or placenta
- Fetal intraabdominal venous anomaly

ACE, angiotensin converting enzyme; CHD, congenital heart defect; NSAIDs, nonsteroidal anti-inflammatory drugs; NT, nuchal traslucency.

Source: Data from Donofrio, M., Moon-Grady, L., Hornberger, L., Copel, J., Sklansky, M. S., Abuhamad, A., . . . Rychik, J. (2014). Diagnosis and treatment of fetal cardiac disease. A scientific statement from American Heart Association. *Circulation, 129*, 2183–2242. doi:10.1161/01.cir.0000437597.44550.5d

The color of the newborn should be observed. Cyanosis is the bluish color of the skin, mucous membranes, and nail beds that occurs when there is at least 5 g/100 mL of deoxygenated hemoglobin in circulation. If cyanosis is present, note whether it is peripheral or central and whether it improves, stays the same, or becomes worse with crying. Cyanosis can result from pulmonary, hematologic, central nervous system, or metabolic diseases, as well as from cardiac defects. Pulmonary and cardiac defects are the two most common causes of central cyanosis in the newborn.

Pallor may indicate vasoconstriction resulting from congestive heart failure (CHF) or circulatory shock caused by severe anemia.

TABLE 7.1

MATERNAL CONDITIONS AND ASSOCIATED FETAL CARDIAC DISEASE

Condition	Defect
Maternal Disease	
Diabetes mellitus	Cardiomyopathy, TGA, VSD, PDA
Lupus erythematosus	Congenital heart block
Collagen disease	Congenital heart block
Congenital heart defect	Increased risk for congenital heart defect (3%–4%)
Viral Disease	
Rubella	
First trimester	PDA, pulmonary artery branch stenosis
Later	Various cardiac and other defects
Cytomegalovirus	Various cardiac and other defects
Herpes virus	Various cardiac and other defects
Coxsackie virus B	Cardiomyopathy
Drugs	
Amphetamines	VSD, PDA, ASD, TGA
Phenytoin	PS, AS, COA, PDA
Trimethadione	TGA, TOF, HLHS
Progesterone/ estrogen	VSD, TOF, TGA
Alcohol	VSD, PDA, ASD, TOF

AS, aortic stenosis; ASD, atrial septal defect; COA, coarctation of the aorta; HLHS, hypoplastic left heart syndrome; PDA, patent ductus arteriosus; PS, pulmonary stenosis; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

Source: Data from Park, M. K. (2014). *Pediatric cardiology for practitioners.* Chicago, IL: Mosby.

Prolonged physiologic jaundice may occur in infants with CHF or congenital hypothyroidism, which is associated with PDA and pulmonary stenosis (PS). A ruddy or plethoric appearance is often seen in polycythemia. These infants may appear cyanotic without significant arterial desaturation.

The presence of significant diaphoresis, particularly with feeding, is very suggestive of a CHD in the newborn. The cause of sweating is sympathetic overactivity as a compensatory mechanism for decreased CO (Park, 2014).

TABLE 7.2

CONGENITAL HEART DEFECTS ASSOCIATED WITH SPECIFIC GENETIC OR CHROMOSOMAL ABNORMALITIES

Disease or Syndrome	Defect
Trisomy 13, 18	PDA, VSD
Trisomy 21	AVC, VSD, PDA
Marfan syndrome	MVP, aortic dilation, and/or aneurysm
Noonan's syndrome	PS, HCM
Turner syndrome	BAV, COA
Williams syndrome	Supravalvar AS and PS
Deletion 22q11 DiGeorge sequence Velocardiofacial syndrome	Conotruncal defects (Truncus, TOF, IAA-B, aortic arch anomalies)

AS, aortic stenosis; AVC, atrioventricular canal defect; BAV, bicuspid aortic valve; COA, coarctation of the aorta; HCM, hypertrophic cardiomyopathy, IAA, interrupted aortic arch; MVP, mitral valve prolapse; PDA, patent ductus arteriosus; PS, pulmonic stenosis; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

Sources: Data from Park, M. K. (2014). *Pediatric cardiology for practitioners.* Chicago, IL: Mosby; Goldmuntz, E., & Crenshaw, M. L. (2016). Genetic aspects of congenital heart defects. In H. D. Allen, R. E. Shaddy, D. J. Penny, T. F. Feltes, & F. Cetta (Eds), *Moss and Adams heart disease in infants, children and adolescents* (9th ed., Vol. 1, pp. 87–116). Philadelphia, PA: Lippincott Williams & Wilkins.

Palpation

Palpation includes the palpation of the precordium and peripheral pulses. Palpation of the precordium detects a thrill, hyperdynamic activity, and the point of maximal impulse (PMI). Irregularities or inequalities of rate or volume can be detected by counting the peripheral pulse rate. Evaluation of the carotid, brachial, femoral, and pedal pulses detects differences between right and left sides and upper and lower extremities. If pulses are unequal, four extremity blood pressures should be measured. Strong arm pulses with weak leg pulses suggest coarctation of the aorta (COA; Park, 2014).

Heart defects that lead to "aortic runoff," or diastolic reversal of flow in the descending aorta, such as PDA, aortic insufficiency, large arteriovenous malformations, or truncus arteriosus, may cause bounding pulses. Preterm newborns frequently have a bounding pulse secondary to relatively decreased subcutaneous tissue and/or PDA. Cardiac failure or circulatory shock causes weak or thready pulses (Park, 2014).

The hyperdynamic precordium indicates a heart defect with volume overload, such as CHDs with large left-to-right shunts (e.g., PDA, VSD) or valvular regurgitation (e.g., aortic regurgitation or mitral regurgitation). The location of the PMI depends on whether the RV or LV is dominant. With RV dominance, the PMI is at the lower left sternal border (LLSB). LV dominance places the PMI at the apex. A diffuse, slow-rising PMI is called a *heave* and is associated with volume overload. A sharp, fast-rising PMI is called a *tap* and is associated with pressure overload. The normal newborn has RV dominance. The LV apical impulse of the newborn is normally felt in the fourth intercostal space to the left of the midclavicular line. Lateral or downward displacement of the apical impulse may indicate cardiac enlargement (Park, 2014).

The presence and location of a thrill provides important diagnostic information. The palms of the hands, rather than the fingertips, should be used to feel for a thrill, except in the suprasternal notch and carotid arteries. The examiner should palpate for the presence of thrills in the upper left, upper right, and LLSB, in the suprasternal notch, and over the carotid arteries. A thrill in the upper left sternal border is derived from the pulmonary valve or pulmonary artery. Thrills in the LLSB suggest PS, or occasionally PDA. A thrill felt in the upper right sternal border signifies aortic origin, usually AS, or, less frequently, PS, PDA, or COA. A thrill over the carotid arteries along with a thrill in the suprasternal notch suggest COA or AS, or other defects of the aorta or aortic valve (Park, 2014).

Palpation of the abdomen is performed to determine the size, consistency, and location of the liver and spleen. Increased liver size is a frequent finding with CHF (Park, 2014).

Auscultation

Careful auscultation by a skilled evaluator is an essential component of any cardiovascular assessment. Auscultation includes HR and regularity, heart sounds, systolic and diastolic sounds, and heart murmurs. The skillful evaluation of cardiac sounds requires systematic auscultation and much practice.

Identification of Heart Sounds

Individual heart sounds should be identified and evaluated before evaluation of cardiac murmurs is attempted. There are four individual heart sounds: S_1, S_2, S_3, and S_4. However, S_3 and S_4 are rarely heard in the newborn. S_1 is the sound resulting from the closure of the mitral and tricuspid valves following atrial systole and is best heard at the apex or LLSB. S_1 is the beginning of ventricular systole. Splitting of S_1 is infrequently heard in newborns. Wide splitting of S_1 is heard in the right bundle branch block or Ebstein anomaly (Park, 2014).

S_2 is the sound created by closure of the aortic and pulmonary valves, which marks the end of systole and the beginning of ventricular diastole. S_2 is best heard in the upper left sternal border or pulmonic area. Evaluation of the splitting of S_2 is important diagnostically. The volume of blood ejected from the aorta and pulmonary artery and the resistance against which the ventricles must pump determine the timing of the closure of the aortic and pulmonary valves. In the immediate newborn period, there may be no appreciable splitting of S_2. Because the RV and LV pump similar quantities of blood and the pulmonary pressure is close to the aortic pressure, these valves close almost simultaneously. Thus, S_2 is heard as a single sound. As the pulmonary vascular resistance decreases, the pulmonary resistance becomes lower than the aortic pressure, causing a splitting of S_2 as the valve leaflets on the left side of the heart (aortic valve) close before those on the right (pulmonary valve). By 72 hours of life, S_2 should be split. The absence of a split S_2 or the presence of a widely split S_2 usually indicates an abnormality. A fixed, widely split S_2 occurs in conditions that prolong RV ejection time or shorten LV ejection time. It occurs in (1) atrial septal defect (ASD) and

partial anomalous pulmonary venous return (PAPVR; amount of blood ejected by RV is increased, resulting in volume overload); (2) PS (stenosis delays right ventricular ejection time, resulting in pressure overload); (3) right bundle branch block (delayed electrical activation of RV); and (4) mitral regurgitation (decreased forward output, decreased LV ejection time; Park, 2014).

A narrowly split S_2 occurs when there is early closure of the pulmonary valve (pulmonary hypertension) or a delay in aortic closure. A single S_2 is significant because it could represent the presence of only one semilunar valve (e.g., aortic atresia [AA], pulmonary atresia [PA], or truncus arteriosus). A single S_2 may also occur with critical PS, in which the pulmonary closure is not audible. Severe AS may also cause a single S_2 because aortic closure is delayed. Severe pulmonary hypertension may cause early closure of the pulmonary valve, thus causing a single S_2.

The relative intensity of the aortic and pulmonary components of S_2 must be assessed. In the pulmonary area (upper left sternal border), the aortic component is usually louder than the pulmonary component. Increased intensity of the pulmonary component, compared with the aortic component, occurs with pulmonary hypertension. Conditions that cause decreased diastolic pressure of the pulmonary artery (e.g., critical PS, TOF, tricuspid atresia) may cause decreased intensity of the pulmonary component. Evaluation of intensity and splitting of S_2 is difficult, particularly in newborns with faster hearts, and requires frequent practice listening to heart sounds (Park, 2014).

As discussed, S_3 and S_4 are rarely heard in the neonatal period; their presence denotes pathologic origin. Likewise, a gallop rhythm, the result of the presence of S_3 or S_4 gallop, is abnormal and associated with CHF (Park, 2014).

After evaluation of individual heart sounds, the systolic and diastolic sounds are evaluated. The ejection sound, or click, occurs after S_1 and may sound like splitting of S_1. The ejection click is best heard at the upper left or right sternal border. The pulmonary click can best be heard at the second or third left intercostal space and is louder with expiration. The aortic click, best heard at the second right intercostal space, does not change in intensity with change in respiration. Ejection clicks are associated with PS or AS or with the dilated great arteries seen in systemic or pulmonary hypertension (Park, 2014).

CARDIAC MURMURS

Cardiac murmurs should be evaluated for intensity (grades 1–6), timing (systolic or diastolic), location, transmission, and quality (musical, vibratory, or blowing).

The grade scale for murmurs is as follows:

Grade 1: barely audible
Grade 2: soft but easily audible
Grade 3: moderately loud, no thrill
Grade 4: loud, thrill present
Grade 5: loud, audible with stethoscope barely on chest
Grade 6: loud, audible with stethoscope near chest

The murmur grade is recorded as 1/6, 2/6, and so on. Again, practice in auscultation improves the practitioner's evaluation skills. The intensity of the murmur is affected by CO; anything that increases CO (e.g., anemia, fever, exercise) increases the intensity of the murmur (Park, 2014).

The next step in evaluating a murmur is its classification in relation to S_1 and S_2. There are three types of murmurs: systolic, diastolic, and continuous.

Systolic Murmurs

The majority of heart murmurs are systolic, occurring between S_1 and S_2. Systolic murmurs are either ejection or holosystolic murmurs. Systolic ejection murmurs (SEMs) occur after S_1 and end before S_2, and are a result of blood flow through narrowed or deformed semilunar valves or increased flow through normal semilunar valves. SEMs are best heard at the second left or right intercostal space. Regurgitant and holosystolic murmurs begin with S_1, with no interval between S_1 and the beginning of the murmur, and continue throughout systole. These murmurs are caused by flow of blood from a chamber at a higher pressure than the receiving chamber throughout systole. Regurgitant and holosystolic murmurs are typically associated with mitral and tricuspid regurgitation and ventricular septal defects (VSDs; Park, 2014).

Location

The location of the maximal intensity of the murmur is helpful in evaluation of the cardiac murmur. Figure 7.3 shows the locations at which various systolic murmurs can be heard.

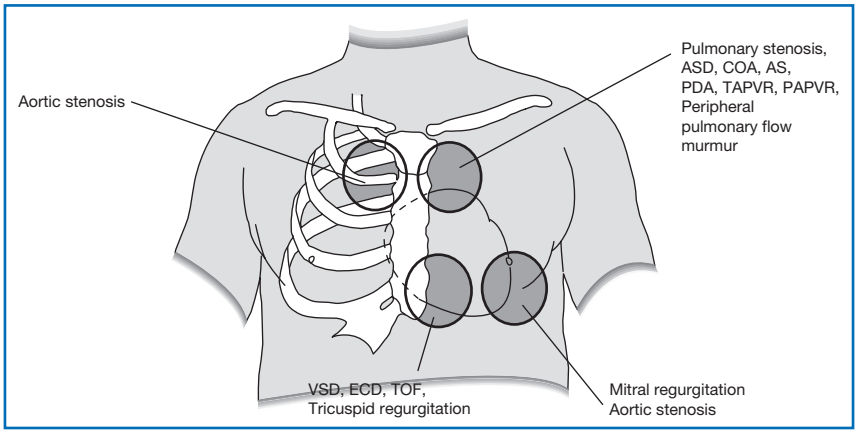

FIGURE 7.3 Location of systolic murmurs.

AS, aortic stenosis; ASD, atrial septal defect; COA, coarctation of the aorta; ECD, endocardial cushion defect; PAPVR, partial anomalous pulmonary venous return; PDA, patent ductus arteriosus; TAPVR, total anomalous pulmonary venous return; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

Related to the location is the radiation of the murmur. Knowledge of radiation of the murmur can help determine the origin. A SEM that radiates well to the neck is usually aortic in origin, whereas one that radiates to the back is usually pulmonic in origin. An apical systolic murmur that radiates to the left axilla and lower back is characteristic of mitral regurgitation, but one that radiates to the upper right sternal border and neck is likely to be aortic in nature (Park, 2014).

Quality

Murmurs are described as musical, vibratory, or blowing (Park, 2014). VSDs or mitral regurgitation murmurs have a high-pitched, blowing quality. AS and PS murmurs have a rough, grating quality. Establishing the quality of the murmur is subjective, and expertise is gained only after extensive practice and experience.

Diastolic Murmurs

Diastolic murmurs occur between S_1 and S_2. Diastolic murmurs are classified according to their timing in relation to heart sounds as early diastolic, middiastolic, or presystolic.

Early diastolic (protodiastolic) murmurs occur early in diastole, right after S_2, and are caused by incompetence of the aortic or pulmonary valve. Aortic regurgitation murmurs are high pitched and are best heard with the diaphragm of the stethoscope at the third left intercostal space. Aortic regurgitation murmurs radiate to the apex. Bounding pulses are present with significant aortic regurgitation. Aortic regurgitation murmurs occur with the bicuspid aortic valve. Pulmonary regurgitation murmurs are medium pitched unless pulmonary hypertension is present, in which case they are high pitched. Diastolic regurgitation murmurs are heard best at the second left intercostal space, radiating along the left sternal border. Pulmonary regurgitation murmurs are common with postoperative TOF and pulmonary valvotomy for PS, or other deformities of the pulmonary valve where there is no competent pulmonary valve and severe or free pulmonary insufficiency (Park, 2014).

Middiastolic murmurs result from abnormal ventricular filling. These murmurs are low pitched and can best be heard with the bell of the stethoscope placed lightly on the chest wall. The murmur results from turbulent flow caused by stenosis of the tricuspid or mitral valve. Mitral middiastolic murmurs are best heard at the apex and are referred to as *apical rumbles*. Mitral middiastolic murmurs are associated with mitral stenosis or large VSDs with a large left-to-right shunt or PDA, producing relative mitral stenosis secondary to increased flow across the normal-sized mitral valve. Tricuspid middiastolic murmurs can best be heard along the LLSB and are associated with moderate to large ASDs, PAPVR or TAPVR, or abnormal stenosis of the tricuspid valve. Presystolic or late diastolic murmurs result from flow through AV valves during ventricular diastole as a result of active atrial contraction ejecting blood into the ventricle. These are low-frequency murmurs found with true mitral or tricuspid valve stenosis (Park, 2014).

Continuous Murmurs

Continuous murmurs begin in systole and continue throughout S_2 into all or part of diastole. Continuous murmurs are caused by (1) aortopulmonary or AV connection (e.g., PDA, AV fistula), (2) disturbances of flow in veins (e.g., venous hum), and (3) less commonly by disturbances of flow in arteries (e.g., severe COA or pulmonary artery stenosis; Park, 2014).

PDA is the most commonly heard continuous murmur in the newborn. The PDA murmur is described as a machinery murmur, louder during systole, peaking at S_2, and decreased in diastole. PDA murmurs are loudest in the left infraclavicular area or the upper left sternal border (Park, 2014).

Other Murmurs

Functional or innocent cardiac murmurs are common in newborns and in school-age children. Innocent murmurs occur in the absence of abnormal cardiac structures. Functional murmurs are asymptomatic. The presence of any unusual or abnormal finding warrants further evaluation with cardiac consultation. Findings such as cyanosis, enlarged heart size on examination or enlarged cardiac silhouette on chest radiograph, abnormal ECG, diastolic murmur, a loud murmur (grade 3/6 systolic murmur or associated with a thrill), weak or bounding pulses, or other abnormal heart sounds have pathologic origins and must be investigated (Park, 2014).

Peripheral pulmonary stenosis murmur or pulmonary flow murmur of infancy is commonly auscultated in newborns. The murmur is thought to be secondary to anatomic discrepancy in size between the main pulmonary artery (MPA) and the branch pulmonary arteries or the angle of takeoff of the branch pulmonary arteries. In utero, the lungs only receive 5% to 10% of the RV CO, so the branch pulmonary arteries are relatively small compared to the MPA since most of the flow shunts from the PA to the ductus to return to the placenta via the umbilical artery. The increased flow after birth creates turbulence in the small vessels, which is transmitted along the smaller branches of the pulmonary arteries. This murmur is best heard at the upper left sternal border with grade of 1/6 to 2/6 intensity radiating to the right and left chest, both axillae, and back. There are no other significant cardiac findings. Typically, it is no longer present after 3 to 6 months of age, and persistence beyond this period should lead to further evaluation for true pathologic peripheral pulmonary artery stenosis (Park, 2014).

CONGENITAL HEART DEFECTS

Etiology

Cardiac development typically is completed by 8 weeks of gestation. Most CHDs are classified as multifactorial (85%), whereas some are associated with chromosomal abnormalities (10%–12%), genetic (1%–2%), or maternal or environmental factors (1%–2%; Wernovsky & Gruber, 2005).

Many chromosomal abnormalities are associated with structural heart defects. Approximately 50% of newborns with trisomy 21 (Down syndrome) have CHD, most commonly ECD, ASD, VSD, and TOF with and without an AVC defect (Goldmuntz & Crenshaw, 2016).

Maternal or environmental factors include maternal illness and drug ingestion. Maternal rubella during the first 7 weeks of pregnancy carries a 50% risk of congenital rubella syndrome (CRS) with major defects of multiple organ systems. Heart defects include PDA and branch pulmonary artery stenosis. Other viral diseases, such as cytomegalovirus, or protozoal diseases, such as toxoplasmosis, are also associated with CHDs. The diagnosis of CHD calls for a careful maternal history to identify viral-like illnesses that may have been unrecognized or unreported at the time of occurrence and careful examination to rule out the presence of other congenital defects (Park, 2014; Seidman, Pyeritz, & Seidman, 2012).

Maternal drug use may also cause cardiac malformations. Fifty percent of newborns with fetal alcohol syndrome (FAS) have CHD. Only a few drugs are proven teratogens (e.g., thalidomide); however, *no* drugs are known to be completely safe.

Metabolic disease of the mother increases the risk for CHDs. Infants of diabetic mothers have a 3% to 5% risk of having CHD (double outlet right ventricle [DORV], truncus, *d*-transposition of the great arteries [TGA], hypoplastic left heart syndrome [HLHS], VSD) and 30% risk of hypertrophic cardiomyopathy (Hornberger, 2006; Rychik, 2012).

Most CHDs are considered to be of multifactorial origin; these defects are probably the result of an interaction effect of the other causes. Research into genetic causes of cardiac defects may identify specific genetic causes for some heart defects that are currently thought to have multifactorial origin. Infants with other congenital defects often have associated CHDs. Multiple congenital defects affect the development of structures that are forming at the time, resulting in interference with normal fetal development.

Incidence

Estimates of incidence of CHD vary from 4 to 10.2 per 1,000 live births. The overall incidence of CHD is slightly less than 1%, or 8 per 1,000 live births, excluding PDA in the preterm newborn (Nouri, 1997; Park, 2014; Webb et al., 2012). CHD accounts for 30% to 50% of mortality of congenital anomalies in infancy, with HLHS accounting for the highest percentage of these deaths (Gilboa, Salemi, Nembhard, Fixler, & Correa, 2010).

Although only 50% of CHD is detected prenatally (Quartermain et al., 2015), with the introduction of pulse oximetry screening for CHD it is expected that the majority of CHDs will be detected earlier or at least before discharge from the newborn nursery. Some of these defects will require surgery in the neonatal period while others may be medically managed. The following discussion of CHDs extends beyond the neonatal period. Table 7.3 is an overview of the diagnosis of CHD.

The discussion of defects is based on the common pathophysiologic features. CHDs can be classified in numerous ways. The simplest classification is based on whether the defect produces cyanosis, a method described by Dr. Helen Taussig in 1947. Cyanosis is the bluish discoloration of the skin that occurs when there is approximately 5 g/100 mL of desaturated hemoglobin in the circulating volume (Taussig, 1947). Thus, the appearance of cyanosis depends on the hemoglobin concentration. An infant with low hemoglobin may be hypoxic but may not appear cyanotic; thus, low

TABLE 7.3

DIAGNOSIS OF CONGENITAL HEART DEFECTS

Defect	Chest Radiograph	Electrocardiogram	Echocardiogram	Catheterization
PDA	Cardiomegaly, increased pulmonary vascularity	In large PDAs: LA enlargement and LV hypertrophy	PDA size, shunt direction, LA/LV dilation, LA/Ao ratio, diastolic reversal of flow in descending aorta	Increased O_2 saturation in pulmonary artery; increased RV and pulmonary artery pressure (with pulmonary hypertension)
VSD	Cardiomegaly, increased pulmonary vascularity	Moderate VSD: LVH and LA enlargement, large VSD: BVH +/− LA enlargement	VSD type/location, size, and number, shunt direction, LA/LV dilation	Increased O_2 saturation in RV, evaluation for elevated pulmonary pressures
ASD	Cardiomegaly, increased pulmonary vascularity	Right axis deviation; RV hypertrophy or RBBB	ASD type and size, shunt direction, RA/RV dilation	Increased O_2 saturation in RA; normal right side pressure; 10% PAPVR
ECD/AVC	Cardiomegaly, increased pulmonary vascularity	Left axis deviation; LA enlargement; RVH; incomplete RBBB	Primum ASD and inlet VSD size, regurgitation of AV valves, RV/LV outflow tract obstruction	Increased O_2 saturation in RA; increased right ventricular and/or pulmonary artery pressure; with angiography, a "goose neck" deformity of ventricular outflow area
PS	Normal heart size; normal pulmonary vascularity; enlarged pulmonary artery	Right axis deviation; RA enlargement; RVH	PS gradient (mild, moderate, or severe), level of obstruction: subvalvar, valvar, supravalvar	Evaluation of level of RVOT obstruction, gradient from RV across the pulmonary artery
TOF	Normal heart size; boot-shaped contour; decreased pulmonary markings; prominent aorta; right aortic arch in 13 cases	Right axis deviation; RVH	VSD size and number, overriding aorta, PS gradient (mild, moderate, or severe), level of obstruction: valvar, subvalvar; size of right and left pulmonary arteries, arch sidedness, coronary artery patterns	Demonstrates anatomy of right ventricular outflow region, VSD directionality, coronary pattern
PA/IVS	Normal heart size or cardiomegaly; decreased pulmonary vascularity	LVH, RA enlargement, occasionally RVH	PA, size of TV, tricuspid regurgitation, RV coronary fistula, branch pulmonary artery size, PDA	RV angiogram to evaluate for presence of coronary sinusoids, radiofrequency perforation of pulmonary valve in two-ventricle approach

(*continued*)

TABLE 7.3

DIAGNOSIS OF CONGENITAL HEART DEFECTS (*continued*)

Defect	Chest Radiograph	Electrocardiogram	Echocardiogram	Catheterization
TAPVR	Cardiomegaly; increased pulmonary vascularity	RVH, RA enlargement	TAPVR connections, RA/RV dilation, pulmonary HTN, PFO right to left	Higher O_2 saturation in right atrium; angiography reveals abnormal pulmonary venous return
AS	Normal heart size; slight prominence of left ventricle and aorta in older kids	Normal in mild cases, LVH with strain in severe obstruction	Aortic valve morphology, level of obstruction in LVOT, LVH, LV function	Performed to evaluate level of LVOT obstruction and gradient, LV end diastolic pressure
COA	Cardiomegaly, pulmonary edema	RVH or RBBB in infants, LVH in older kids	Transverse arch size, discrete or long segment coarctation, LV function, bicuspid aortic valve, mitral valve abnormality, LVOT obstruction	In infants, performed in patients with recurrent obstruction after surgery
HLHS	Cardiomegaly; increased pulmonary vascularity	RVH	HLHS subtype: AS or AA, MA or MS, ascending aorta size, ASD size, RV function, TR	Balloon atrial septostomy and stenting if ASD is inadequate.
TGA	Cardiomegaly; increased pulmonary vascularity	Right axis deviation; RVH	Aortic outflow arises from RV, ASD size, coronary pattern, RV or LV outflow tract obstruction, presence of a VSD	Balloon atrial septostomy if ASD is inadequate. Increased right ventricular pressure; catheter can enter aorta from right ventricle; pulmonary artery can be entered only through PDA or ASD
Truncus	Cardiomegaly; increased pulmonary vascularity	BVH	Truncus type, truncal stenosis or insufficiency, arch sidedness, VSD size	Left-to-right shunt at level of ventricle; pressure equal in ventricles, truncus, and pulmonary arteries

AA, aortic atresia; AS, aortic stenosis; ASD, atrial septal defect; AVC, atrioventricular canal; BVH, biventricular hypertrophy; COA, coarctation of the aorta; ECG, electrocardiogram; ECD, endocardial cushion defect; HLHS, hypoplastic left heart syndrome; LA, left atrium, LA/Ao, left atrium to aortic root; LV, left ventricle; LVH, left ventricular hypertrophy; LVOT, left ventricular outflow tract; MA, mitral atresia; MS, mitral stenosis; PA/IVS, pulmonary atresia with intact ventricular septum; PAPVR, partial anomalous pulmonary venous return; PDA, patent ductus arteriosus; PFO, patent foramen ovale; PS, pulmonary stenosis; RA, right atrium; RRBB, right bundle branch block; RV, right ventricle; RVH, right ventricular hypertrophy; RVOT, right ventricular outflow tract; TA, truncus arteriosus; TAPVR, total anomalous pulmonary venous return; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

Source: Data from Park, M. K. (2014). *Pediatric cardiology for practitioners.* Chicago, IL: Mosby.

hemoglobin cannot be the sole criterion for determining pathologic origin. Cyanosis in the extremities, or acrocyanosis, is frequently seen in newborns because of reduced blood flow through the small capillaries. Oxygen is extracted from the hemoglobin in the capillaries, giving the skin a blue appearance. This blue appearance is a normal phenomenon in the newborn. Differentiation of central cyanosis from peripheral or acrocyanosis is essential since acrocyanosis is a benign condition while central cyanosis is associated with respiratory, cardiac, or metabolic conditions.

The presence or absence of cyanosis depends on whether or not deoxygenated blood is oxygenated by going through the lungs. CHD lesions that allow the blood to go through the lungs and then shunt from the left side of the heart and back to the right side of the heart are generally acyanotic and typically result in too much pulmonary blood flow. Defects that shunt deoxygenated blood directly to the left side of the heart, bypassing the lungs, are cyanotic heart defects and are typically a result of inadequate pulmonary blood flow. Some defects have mixed anatomic or functional features and do not fit into this schema, or there is overlap between the classifications. For this discussion, the following categories are used: (1) acyanotic defects with a left-to-right shunt due to communication between the systemic and pulmonary circulations typically resulting in too much pulmonary blood flow; (2) cyanotic defects that typically are a result of inadequate pulmonary blood flow; (3) left-sided obstructive defects with inadequate systemic blood flow; and (4) defects with abnormal aortopulmonary connections.

Defects With Left-to-Right Shunts

Typically, these defects have left-to-right shunts with increased pulmonary blood flow and volume overload on the heart. These defects typically result in too much pulmonary blood flow and include PDA, VSD, ASD, and endocardial cushion (ECD) or AV canal defects (AVC).

Patent Ductus Arteriosus

The DA is a vascular connection between the pulmonary artery and the aorta. The DA originates from the main pulmonary artery and enters the aorta distal to the left subclavian artery; it allows deoxygenated blood from the RV to bypass the lungs and enter the descending aorta. The DA functionally closes around 15 hours of life. During the first 24 hours of life, there may be some shunting

of blood, but typically it is insignificant unless the ductal opening is large and remains patent.

Closure of the DA occurs in response to increased arterial oxygen concentration after the initiation of respiratory function. Other factors that contribute to closure of the DA include a decrease in prostaglandin E (PGE) and an increase in acetylcholine and bradykinin (Park, 2014). Closure of the DA occurs within 48 hours in 80% of newborns and close to 100% close within 96 hours. PDA in the preterm newborn presents a different clinical problem and is discussed separately from PDA in the term newborn (Park, 2014; Webb et al., 2012).

Patent Ductus Arteriosus in the Term Newborn

Incidence. PDA accounts for approximately 5% to 10% of all CHDs, excluding those in preterm newborns. There is a higher ratio of PDA in females (about 3:1). PDAs are more common in infants with Down syndrome or those whose mothers had rubella during pregnancy (Park, 2014).

Hemodynamics. In extrauterine life, the flow of blood through the DA is reversed. The PDA allows blood to flow from left to right, thereby reentering the pulmonary circuit and increasing pulmonary blood flow. The amount of blood flow through the PDA and the effects of the ductal flow depend on the difference between systemic and pulmonary vascular resistance and the diameter and length of the ductus.

Over time, high pulmonary blood flow causes increased pulmonary vascular resistance, pulmonary hypertension, and right ventricular hypertrophy. Figure 7.4 depicts the hemodynamics of PDA.

Manifestations. A small PDA may be asymptomatic. A large PDA with significant shunting may cause signs of CHF including tachypnea and poor feeding. Frequent lower respiratory tract infections, poor feeding, and poor weight gain are common in older infants with PDA.

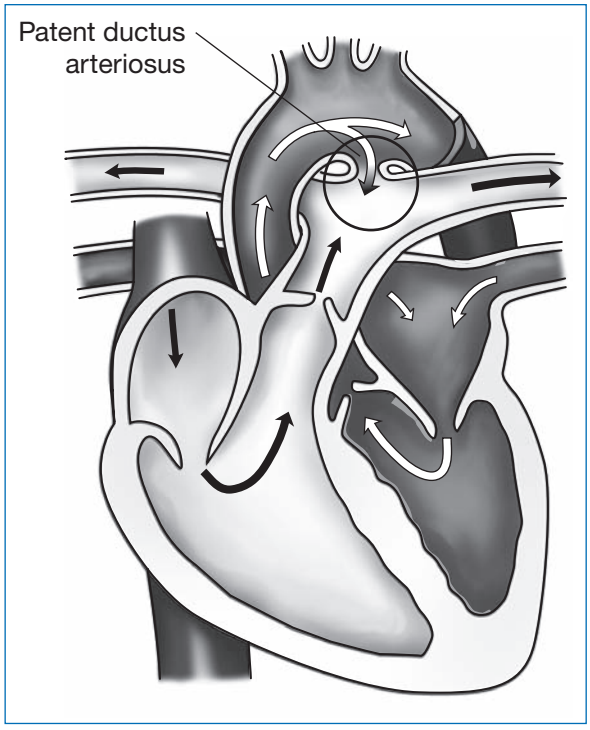

FIGURE 7.4 Patent ductus arteriosus is a communication between the pulmonary artery and the aorta.

Source: Adapted and modified from Ross Laboratories, Columbus, OH, Clinical Education Aid, 1985.

Diagnosis. The diagnosis of PDA is based on history and physical examination findings, chest radiograph, and echocardiogram. Characteristic findings on physical examination include bounding peripheral pulses, widened pulse pressure (>25 mmHg), and a hyperdynamic precordium. A systolic thrill may be felt at the upper left sternal border. A grade 1/6 to 4/6 continuous "machinery" murmur is audible at the upper left sternal border or left infraclavicular area. The murmur is heard throughout the cardiac cycle because of the pressure gradient between the aorta and the pulmonary artery in both systole and diastole. In cases of a large PDA with a significant shunt, the S_2 may be accentuated because of pulmonary hypertension (Park, 2014; Webb et al., 2012).

A small PDA may not be distinguishable on chest radiograph. With more significant shunting, there may be cardiomegaly and increased pulmonary vascularity. An ECG may demonstrate left atrial enlargement and left ventricular hypertrophy and an abnormal QRS axis, more leftward, for age. The definitive diagnosis is made by echocardiogram. Echocardiogram demonstrates size and directionality of PDA, LA to aortic ratio (LA/Ao ratio), presence of LA and LV dilation, arch sidedness, diastolic flow reversal in the descending aorta, ventricular function, and pulmonary hypertension.

Management. The treatment of the clinically significant PDA is medical or surgical closure. However, there is no absolute agreement on the criteria for determining clinical significance in the term newborn. If the term newborn's signs and symptoms are not affecting feeding and weight gain, a conservative approach to management may be used because the ductus may close over time on its own. Conservative treatment includes fluid management, diuretics, and close observation to assure that the baby is feeding well and gaining weight. The incidence of spontaneous closure decreases as the infant becomes older. **Quality and Safety: If the newborn exhibits signs of increased pulmonary blood flow, such as respiratory distress or inability to feed, closure of the PDA is indicated.** Closure by medications is not effective in term infants; so, a clinically symptomatic PDA requires transcatheter closure with a coil or device in the cardiac catheterization laboratory. Surgical ligation through a posterolateral thoracotomy is the preferred method of closure in cases of large PDAs or if there are structural challenges due to anatomic variations. The mortality rate for surgical ligation is less than 1% (excluding preterm newborns). The prognosis is excellent, and complications are rare (Park, 2014; Webb et al., 2012).

Patent Ductus Arteriosus in the Preterm Newborn

PDA is a common complicating factor in the care of preterm newborns. As the newborn recovers from respiratory distress, pulmonary vascular resistance decreases as oxygenation improves. The ductus arteriosus in the preterm newborn is not as responsive (compared to term newborns) to increased oxygen content and will remain patent. Decreased pulmonary vascular resistance causes blood to shunt from left to right, resulting in increased pulmonary blood flow and pulmonary venous congestion, which decreases lung compliance. Consequences of large PDA shunts include CHF symptoms, inability to wean ventilatory support, and/or increased oxygen requirement.

Clinical findings indicative of PDA include bounding peripheral pulses, hyperdynamic precordium, widened pulse pressures (>25 mmHg), and a continuous murmur, best heard at the upper left and middle sternal borders. Chest radiograph findings include increased pulmonary vascularity and pulmonary edema along with cardiomegaly. An echocardiogram provides diagnostic imaging for

a PDA including size, directionality, LA/Ao ratio, presence of LA and LV dilation, arch sidedness, diastolic flow reversal in the descending aorta, ventricular function, and pulmonary hypertension (Park, 2014; Webb et al., 2012).

Management of PDA depends on the severity of the symptoms. In asymptomatic or mildly symptomatic newborns, conservative management may be elected to allow for spontaneous closure, since one third of extremely low birthweight (ELBW) neonates undergo spontaneous PDA closure. Conservative management consists of fluid restriction, diuretic therapy, and careful monitoring (Koch et al., 2006; Park, 2014).

In symptomatic and/or ventilator-dependent preterm newborns, closure of the DA may improve oxygenation and has been associated with decreased complications of prematurity (Koch et al., 2006). Two medications can be used to promote ductal closure. Indomethacin is a prostaglandin synthetase inhibitor. PGE_2 is produced in the walls of the DA to prevent closure during fetal life. Indomethacin inhibits the production of PGE_2 and promotes ductal closure. Smaller babies may require a higher dose to obtain effective plasma levels. Indomethacin is highly nephrotoxic; so, the blood urea nitrogen (BUN) and creatinine (Cr) levels must be followed to monitor renal function. Contraindications to using indomethacin include renal failure, low platelet count, bleeding disorders, necrotizing enterocolitis (NEC), and hyperbilirubinemia (Park, 2014; Webb et al., 2012). Ibuprofen is an alternative to indomethacin for closure of the DA in preterm infants. Both medications are equally effective in closure of PDA and have similar adverse effects on renal function (Kushnir & Pinheiro, 2011; Sekar & Corff, 2008). Surgical ligation is reserved for cases where indomethacin or ibuprofen fails or is contraindicated. Mortality from surgical ligation is highest in the more preterm, sicker infants, especially if pulmonary hypertension has developed (Park, 2014; Webb et al., 2012). Associated complications of short- and long-term outcomes of ligation, such as ND outcomes, must be considered in the selection of PDA management.

Ventricular Septal Defect

A VSD is a defect or opening in the ventricular septum caused by inadequate septal formation during early fetal development. There are several types of VSDs that involve the membranous or muscular part of the ventricular septum. The location, size of the defect, and the degree of shunting are important in determining the hemodynamic impact and need for intervention. With a small defect, there is a large resistance to the left-to-right shunt at the defect, and the shunt does not depend on the pulmonary vascular resistance. With a large VSD, there is little resistance at the defect and the amount of left-to-right shunt depends on the level of pulmonary vascular resistance (Park, 2014; Turner, Hunter, & Wyllie, 1999; Webb et al., 2012).

Incidence. VSD is the most common CHD in children. It accounts for approximately 20% to 25% of all CHDs.

Hemodynamics. The hemodynamic consequences of a VSD depend on its size: small, moderate, or large.

Small VSD. Small VSDs produce minimal shunting and may not be symptomatic. Chest radiograph and ECG are generally normal. A loud high-frequency holosystolic heart murmur may be best heard in the third and fourth left intercostal spaces at the sternal border (Park, 2014; Turner et al., 1999; Webb et al., 2012). Figure 7.5 shows a VSD.

Moderate VSD. With moderate-sized VSDs, the blood is shunted from the LV to RV because of higher pressure in the LV and higher systemic vascular resistance. The shunt of blood occurs during systole, when the RV contracts, such that the blood enters the pulmonary artery rather than remaining in the RV.

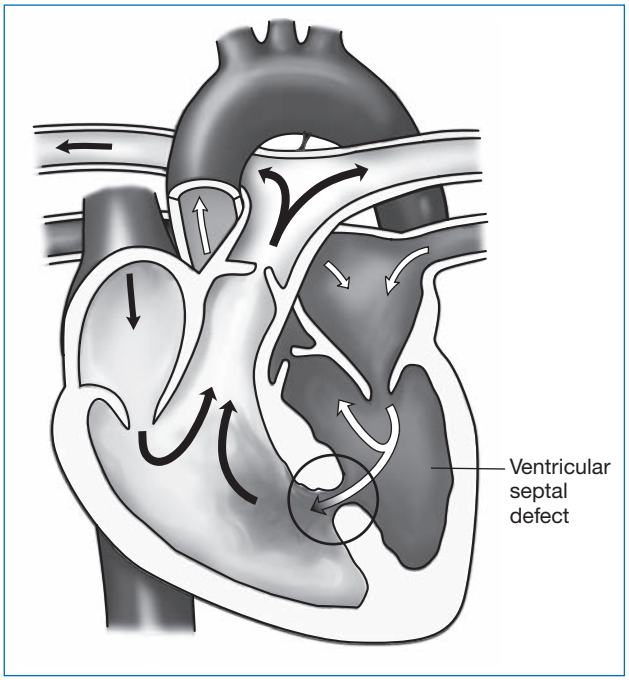

FIGURE 7.5 Ventricular septal defect is a communication between the right and left ventricles.

Source: Adapted and modified from Ross Laboratories, Columbus, OH, Clinical Education Aid, 1985.

Large VSD. With large VSDs, blood is shunted from the LV to RV. The volume of blood shunted is related to the size of the VSD and the pulmonary vascular resistance. The larger the VSD, the greater the volume of blood shunted, and the higher the pressure in the RV and pulmonary artery. If pulmonary artery pressure is significantly increased, thickening of the walls of the pulmonary arterioles may develop, and the increased resistance may decrease the left-to-right shunt. If left untreated, over long periods of time, pulmonary vascular disease can develop and lead to Eisenmenger syndrome with fixed right-to-left shunting resulting in significant cyanosis.

Manifestations. Manifestations of VSD depend on the degree of shunting. Small VSDs may produce no hemodynamic compromise and no clinical symptoms, but will typically be detected by a cardiac murmur on examination. Larger defects are associated with inadequate feeding, poor growth, symptoms of CHF, and can also be associated with recurrent pulmonary infections.

Diagnosis. VSDs typically will have a 2/6 to 4/6 holosystolic murmur best heard at the left sternal border (LSB). There may also be an apical diastolic rumble and the pulmonary heart sound may be loud.

Chest radiograph can help detect moderate to large VSDs (Danford, Gumbiner, Martin, & Fletcher, 2000), demonstrating cardiomegaly as a result of LA and LV dilation and increased pulmonary vascularity and edema. ECG may reveal LV hypertrophy. RV hypertrophy may also be present in severe cases. An echocardiogram will provide information about the location and size of the VSD, directionality of the flow, and presence of LA and LV dilation along with presence of additional VSDs.

Management. Treatment of the VSD depends upon the size of the defect and the resultant cardiovascular symptoms. Spontaneous closure of the VSD can occur; so, infants with hemodynamically insignificant defects may be followed clinically to allow time

for spontaneous closure to occur. Small VSDs generally close spontaneously over the first few years of life. Muscular VSDs have a higher spontaneous closure rate than perimembranous VSDs (29% vs. 69%; Turner et al., 1999).

Quality and Safety: Initial management of the hemodynamically significant VSD includes monitoring for signs of CHF and prompt initiation of therapy. CHF in the older infant is treated with diuretics, angiotensin converting enzyme (ACE) inhibitors, and/or digitalis.

Surgical management involves primary suture or patch closure of the VSD. Cardiopulmonary bypass is required for surgical correction. The timing of the surgery depends on the location and size of the VSD. Large VSDs typically result in a significant left-to-right shunt with left atrial and ventricular dilation and CHF symptoms of poor feeding and inadequate weight gain. **Emergency Alert: If CHF symptoms cannot be medically managed, then this is an indication for surgical repair** (Park, 2014).

The aggregate surgical mortality rate for VSD correction is less than 0.6%. The mortality rate is higher among small infants less than 2 months of age and those with other defects or multiple VSDs (Jacobs et al., 2018; Park, 2014).

Atrial Septal Defect

An ASD is a defect or opening in the atrial septum that develops as a result of inadequate septal formation early in fetal cardiac development.

There are three types of ASDs (Park, 2014; Webb et al., 2012):

1. Ostium secundum ASD
2. Ostium primum ASD, associated with AVC
3. Sinus venosus ASD, typically associated with partial anomalous pulmonary venous connection

Incidence. ASDs account for 5% to 10% of all CHDs.

Hemodynamics. An ASD usually does not produce symptoms until pulmonary vascular resistance begins to decrease and RV end-diastolic and RA pressures decline. All types of ASDs produce some blood flow alterations. With an ASD, blood shunts from left to right across the defect because the RV offers less resistance to filling, due to it being more compliant than the LV. Any factors that decrease RV distensibility or obstruct flow into the RV (e.g., PS or tricuspid stenosis) can reduce or reverse the shunt direction (Massin, Derkenne, & von Bernuth, 1998). The left-to-right shunt increases RV volume, but pulmonary vascular resistance decreases, so pulmonary artery pressure is almost normal. Over long periods of times, typically years, the increased pulmonary blood flow due to a large ASD gradually leads to increased pulmonary artery pressures and CHF in adults (Park, 2014). Figure 7.6 illustrates an ASD.

Manifestations. Newborns with ASDs are usually asymptomatic. In infants and children, a grade 2/6 to 3/6 SEM can best be heard at the upper left sternal border with a fixed, widely split S_2. With a large secundum ASD, there may be a middiastolic rumble caused by the relative tricuspid stenosis audible at the LLSB (Park, 2014; Webb et al., 2012). On chest radiograph, the heart is enlarged with a prominent main pulmonary artery segment and increased pulmonary vascularity. ECG enhances detection of ASD, showing RA deviation, RV hypertrophy, and there may be incomplete right bundle branch block (Danford et al., 2000; Park, 2014).

Diagnosis can be made by echocardiogram, which demonstrates the ASD type, size, and associated RA and RV dilation as a result of a hemodynamically significant left-to-right shunt in moderate to large secundum ASDs.

Management. Untreated ASDs can lead to CHF, pulmonary hypertension, and atrial dysrhythmias in adults. Spontaneous closure of ASDs occurs in the first 5 years of age in up to 40% of children (Park, 2014). ASDs typically are asymptomatic. Large ASDs may result in right-sided dilation, and rarely CHF. Secundum ASDs that are hemodynamically significant with right-sided dilation may be closed using transcatheter device closure in the cardiac catheterization laboratory. This approach is less invasive since it involves access via femoral vein/arteries, does not require cardiopulmonary bypass, and the patient typically can be discharged the next day.

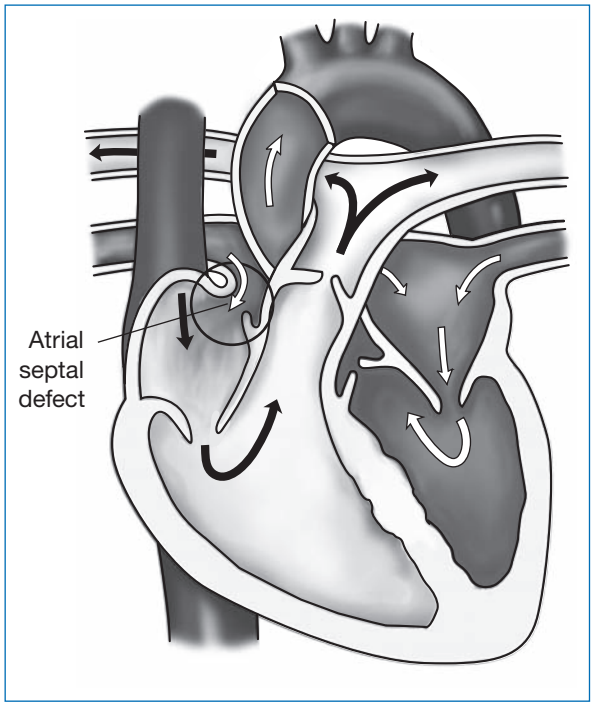

FIGURE 7.6 Atrial septal defect is a communication between the right and left atria.

Source: Adapted and modified from Ross Laboratories, Columbus, OH, Clinical Education Aid, 1985.

Surgical correction is reserved for infants for whom the transcatheter approach is unsuccessful due to the size of the ASD or inadequate septum attachments for the device, for primum ASDs, and sinus venosus ASDs. Surgical correction is accomplished by a simple patch or with direct closure during open-heart surgery using cardiopulmonary bypass. Timing of surgery varies depending on the ASD type, size, and presence of a significant left-to-right shunt with RA and RV dilation. The surgical mortality rate is less than 0.5% with a higher risk for mortality in small infants with CHF or increased pulmonary vascular resistance (Park, 2014; Webb et al., 2012).

Atrioventricular Canal Defects/Endocardial Cushion Defects

ECDs result from inadequate fusion of the endocardial cushions during fetal development, resulting in a common AV valve with an ASD (ostium primum) and inlet VSD. There are three types of AVC: a complete AV canal with a primum ASD and inlet VSD, a transitional AVC with a primum ASD and a restrictive inlet VSD, and an incomplete AV canal with only a primum ASD. The type of AVC is important in the presentation of clinical symptoms and timing of surgery (Park, 2014).

Incidence. AVCs account for 2% of all CHDs. AVCs are common in infants with Down syndrome (Park, 2014).

Hemodynamics. The hemodynamic consequences of AVCs depend on the type of defect. There may be interatrial and interventricular

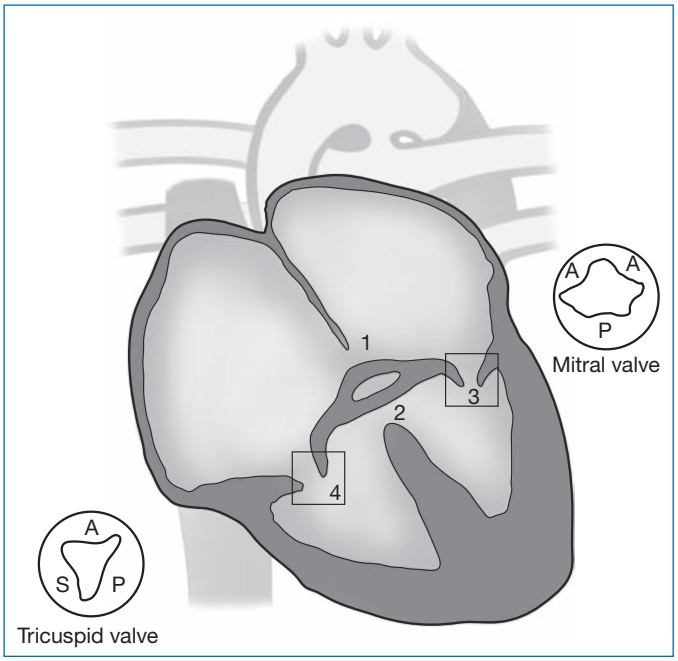

FIGURE 7.7 Endocardial cushion defect. (1) Ostium primum atrial septal defect; (2) a ventricular septal defect in the inlet portion of ventricular septum; (3) cleft in anterior mitral valve leaflet; (4) cleft in septal leaflet of the tricuspid valve, resulting in common anterior and posterior cusps of the atrioventricular valve.

A, anterior; P, posterior; S, septal.

shunts, LV to RA shunts, or AV valve regurgitation. Figure 7.7 shows an ECD.

Manifestations. The manifestations of AVCs result from the increased pulmonary blood flow from left-to-right flow from the VSD and regurgitation of the common AV valves if present. **Emergency Alert: The newborn may have respiratory distress, signs of CHF, tachycardia, and a cardiac murmur. The mitral regurgitation may be heard as a grade 3/6 holosystolic regurgitant murmur audible at the LLSB and may be audible at the apex.** There is also a middiastolic rumble at the LLSB or at the apex caused by the relative stenosis of tricuspid and mitral valves (Freedom, Yoo, & Coles, 2007; Park, 2014).

Chest radiograph reveals generalized cardiomegaly with increased pulmonary vascularity and a prominent main pulmonary artery segment. ECG shows left axis deviation with a prolonged P-R interval, right and left atrial enlargement, right ventricular hypertrophy, and incomplete right bundle branch block. An infant with an AVC may demonstrate signs of CHF with failure to thrive due to poor feeding, inadequate weight gain, and recurrent respiratory infections. Physical examination of an untreated infant with AVC reveals a poorly nourished infant with signs of respiratory distress and tachycardia (Freedom et al., 2007; McElhinney, Paridon, & Spray, 2000; Park, 2014).

Management. Initial medical management is aimed at preventing or treating CHF with diuretics, ACE inhibitor, and/or digitalis. Definitive management consists of surgical closure of the ASD and VSD, with reconstruction of AV valves under cardiopulmonary bypass, or in rare cases, pulmonary artery banding may be performed as a temporizing palliative procedure as part of a two-staged surgical correction.

Surgery is indicated when there is CHF with failure to thrive that is unresponsive to medical therapy and/or a large shunt with development of pulmonary hypertension and increasing pulmonary vascular resistance. Timing of surgical repair depends on the type of defect. Complete AVCs undergo repair around 2 to 4 months of age, sometimes earlier if the CHF symptoms cannot be medically managed. Transitional AVCs typically undergo repair within the first year of life and incomplete AVCs between 1 to 2 years of age, sometimes even older if they are asymptomatic. The aggregate mortality rate is 2.7%. Factors that increase the risks of mortality for AVC repair include (1) very young age, (2) severe AV valve incompetence, (3) hypoplastic left ventricle, and (4) severe symptoms before surgery (Jacobs et al., 2018; Park, 2014).

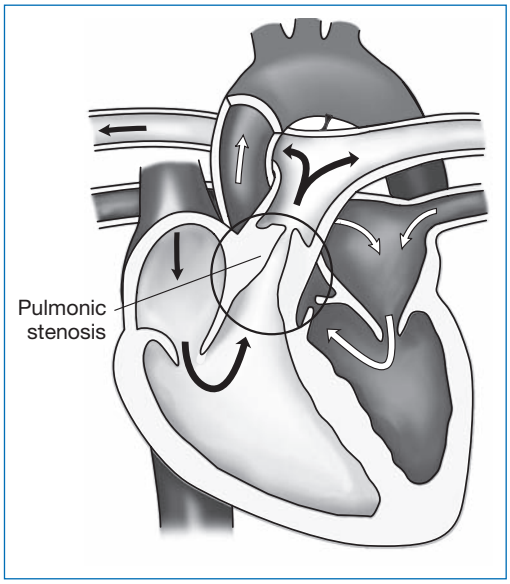

FIGURE 7.8 Pulmonary stenosis.

Cyanotic Defects

These CHDs are defects with obstruction to RV outflow that result in reduced pulmonary blood flow or abnormality in venous return. The defects described in this section include PS, TOF, pulmonary atresia with intact ventricular septum (PA/IVS), and total anomalous pulmonary venous return (TAPVR).

Pulmonary Stenosis

PS is caused by abnormal formation of the pulmonary valve leaflets during fetal cardiac development. PS can be valvular, subvalvular (infundibular), or supravalvular. Valvular PS is the most common, accounting for 90% of cases. PS is frequently seen in Noonan syndrome. It is one of the four defects found in TOF. Isolated infundibular PS is uncommon.

Incidence. PS makes up 5% to 8% of all CHDs. It is often associated with other defects.

Hemodynamics. PS results in obstruction to blood flow from the RV to the pulmonary artery, and there is a spectrum of disease from mild PS to critical PS (duct dependent). In cases of more severe obstruction, the RV hypertrophies in response to the increased pressure caused by the obstruction to outflow. Pulmonary blood flow volume is normal in the absence of intracardiac shunting. PS is shown in Figure 7.8.

Manifestations. PS may be asymptomatic if it is mild or moderate with normal oxygen saturations. Neonates with severe or critical PS may have saturations less than 95%.

Diagnosis. The findings of PS depend on the severity of the defect. A pulmonary systolic ejection click may be heard at the upper

left sternal border and S_2 may be widely split with the pulmonary component soft and delayed. A SEM (grade 2/6–4/6) is audible at the upper left sternal border and radiates to the back. The severity of the PS is directly related to the loudness and duration of the murmur. A systolic thrill can sometimes be felt at the upper left sternal border, which would result in a grade 4/6 SEM.

The ECG is normal in mild PS. There may be right axis deviation and RV hypertrophy with moderate stenosis and right atrial enlargement and RV hypertrophy with strain with severe PS.

Chest radiograph demonstrates normal heart size with a prominent main pulmonary artery segment. In mild to moderate PS, pulmonary markings are normal. The critical type of PS causes decreased pulmonary markings. Echocardiogram evaluation involves determining level of obstruction (subvalvular, valvular and supravalvular), valve morphology, PDA patency, and associated defects. Decreased motion of the pulmonary valve leaflets and poststenotic dilation of the main pulmonary artery segment may be present (Danford, Salaymeb, Martin, Fletcher, & Gumbiner, 1999; Park, 2014).

Management. Management of PS is determined by the severity of the obstruction to flow. The mild type generally requires no therapy unless there is worsening of the PS. Moderate to severe PS is treated through balloon valvuloplasty during cardiac catheterization. Surgical correction is performed in children with critical PS when balloon valvuloplasty is not successful in relieving the gradient, or when the pulmonary valve fails to grow after balloon valvuloplasty. Infants with critical PS require PGE_1 infusion to maintain ductal patency until surgery is performed (Park, 2014).

The overall prognosis for PS is excellent. The mortality rate is less than 1% in older infants. The mortality rate is higher in newborns with critical PS and CHF (Park, 2014).

Tetralogy of Fallot

Edward Fallot, a French physician, first described TOF in 1888. During fetal development, TOF is a result of anterior deviation of the conal septum (wall between the aortic and pulmonary valves), which causes subpulmonary/pulmonary outflow obstruction and a large anterior malalignment VSD. TOF is comprised of four defects: VSD, pulmonary valve stenoisis, overriding aorta, and RV hypertrophy. There is a spectrum of TOF from mild PS with no cyanosis (pink TOF) to PA that is duct dependent.

Incidence. TOF accounts for 10% of all CHDs. TOF is the most common cyanotic heart defect beyond infancy.

Hemodynamics. In TOF, the large VSD causes equalization of pressure in the ventricles. Unsaturated blood flows through the VSD into the aorta because of the obstruction to blood flow from the RV into the pulmonary artery. TOF is illustrated in Figure 7.9.

Manifestations. Newborns may be asymptomatic or may present with a loud murmur and/or cyanosis. Severe decompensation or "tet" spells may occur in infants or children, but these can also occur in neonates. Children instinctively assume a squatting position, which traps venous blood in the legs, decreases systemic venous return to the heart, and increases systemic vascular resistance to increase left-to-right flow (Park, 2014).

Diagnosis. Neonates with TOF exhibit varying degrees of cyanosis, depending on the severity of the obstruction of blood flow through the RVOT. A long, loud, grade 3/6 to 4/6 SEM is heard at the upper left sternal border. A PDA murmur may also be heard in TOF with critical PS or PA (Park, 2014).

Chest radiograph demonstrates decreased or normal heart size with decreased pulmonary vascularity. The contour of the heart may be boot-shaped due to the concave main pulmonary artery segment with upturned apex. There may also be RA enlargement and some patients may have a right aortic arch.

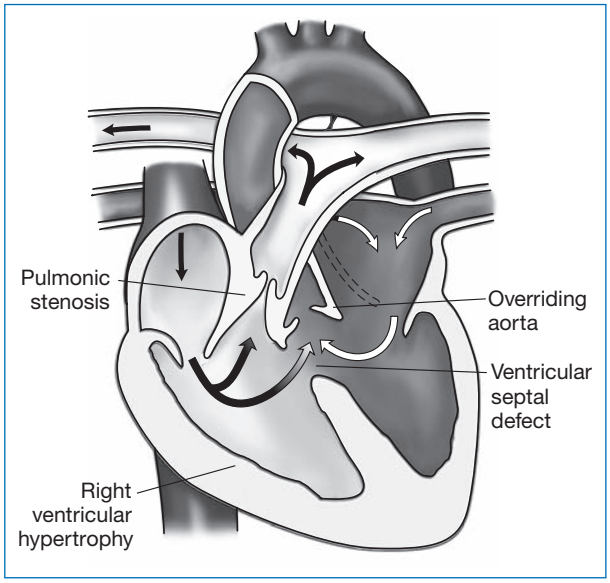

FIGURE 7.9 Tetralogy of Fallot consists of pulmonary stenosis, ventricular septal defect, overriding aorta, and hypertrophy of the right ventricle.
Source: Adapted and modified from Ross Laboratories, Columbus, OH, Clinical Education Aid, 1985.

Echocardiogram demonstrates a large anterior malalignment VSD with overriding aorta, degree of PS and level of RVOT obstruction, coronary artery pattern, and presence of additional VSDs or right aortic arch.

Management. The definitive therapy for TOF is surgical repair under cardiopulmonary bypass. The surgical correction can sometimes be delayed with careful medical management. **Quality and Safety: Careful follow-up is essential to detect signs of clinical deterioration and worsening cyanosis.** Parents need adequate education and support for home management (Dipchand, Giuffre, & Freedom, 1999; Park, 2014).

Parents must be taught how to recognize the early signs and symptoms of decompensation. They must also be taught to recognize and treat hypercyanotic or tet spells (Table 7.4). Tet spells are precipitated by events that lower the systemic vascular resistance, producing a large right-to-left ventricular shunt. Increased activity, crying, nursing, or defecation may trigger a hypoxemic episode. The right-to-left shunt causes a decreased Pao_2, increased $Paco_2$, and decreased pH, which stimulate the respiratory center, causing increased rate and depth of respirations (hyperpnea). The hyperpnea causes increased systemic venous return by increasing the efficiency of the thoracic pump. The RVOT obstruction prevents the increased blood flow from entering the pulmonary artery, so the increased flow is shunted through the VSD to the aorta, which further decreases the arterial Po_2. Severe, uninterrupted hypercyanotic spells lead to loss of consciousness, hypoxemia, seizures, and death.

Surgical treatment is indicated in the presence of hypercyanotic spells (tet spells) that result in increased hypoxemia, metabolic acidosis, inadequate systemic perfusion, and increased cyanosis. Systemic perfusion can be evaluated by observing peripheral pulse intensity, urine output, capillary filling time, blood pressure, or peripheral vasoconstriction.

Surgical management can be either palliative or corrective. Palliative procedures are undertaken to improve pulmonary blood flow by creating a pathway between the systemic and pulmonary circulations. In addition, these procedures allow time for the right

TABLE 7.4

RECOGNITION AND TREATMENT OF TET SPELLS

Manifestations	Treatment	Rationale
Irritability, crying, hyperpnea	Knee to chest or squatting position	Traps blood in lower extremities to decrease systemic venous return; increases pulmonary blood flow
Cyanosis	Oxygen administration	Improves arterial oxygen saturation
Diaphoresis, loss of consciousness	Morphine sulfate (0.1–0.2 mg/kg/dose)	Suppresses respiratory center to decrease hyperpnea
Seizures	Bicarbonate	Corrects acidosis and eliminates stimulation of respiratory center
Decreased murmur	Propranolol (Inderal; 0.15–0.25 mg/kg/dose)	May decrease spasm of right ventricular outflow tract or may act peripherally to stabilize

and left pulmonary arteries to grow. Palliative procedures are indicated for newborns with TOF with PA or critical PS (duct dependent) or children with a hypoplastic pulmonary artery, in whom early corrective surgery may be difficult (Park, 2014).

Surgical correction is performed under cardiopulmonary bypass, and the timing of surgery depends on the cardiac center. Some centers perform complete TOF repair in the neonatal period; some perform palliative surgery for TOF/PA or critical PS with a BT shunt and then complete repair after 6 months of age. The defect is repaired by patch closure of the VSD with widening of the RVOT with a transannular patch if the pulmonary valve is moderate to severely hypoplastic. Postoperative care of the newborn requires careful assessment and monitoring so that complications can be prevented or quickly identified and treated (Russo & Russo, 2005). Complications of cardiac surgery are listed in Tables 7.5 and 7.6. The mortality rate for TOF varies with the severity of the circulatory compromise caused by the defect. The aggregate mortality rate is now 1.1% for uncomplicated TOF. More severe cases have a higher mortality rate, exhibit residual pulmonary outflow tract obstruction, and may require further surgery (Jacobs et al., 2018; Park, 2014).

Pulmonary Atresia With Intact Ventricular Septum

PA/IVS results in the absence of communication between the RV and the pulmonary artery and is a duct-dependent lesion. Determining whether the RV is adequate based on the tricuspid valve annulus size and Z score is important to determine if the neonate will require a single ventricle palliation or two ventricle repair. In addition, evaluation for RV-dependent coronary circulation is important to determine the pathway of single ventricle palliation versus two ventricular repair. If the RV is inadequate and/or there are RV-dependent coronaries, then the patient will require single

TABLE 7.5

COMPLICATIONS OF CARDIAC SURGERY

Low Cardiac Output	*Low Cardiac Output*
Hypovolemia	Pulmonary hypertension
Hemorrhage	Inadequate ventilatory support
Diuresis	Ineffective pleural drainage
Inadequate fluid volume	Hypoventilation secondary to pain
Tamponade	***Renal Dysfunction or Failure***
Mediastinal bleeding	Poor systemic and renal perfusion
Inadequate mediastinal drainage	Intravascular hemolysis
Decreased cardiac contractility	Thromboembolus
Hypervolemia	Nephrotoxic drugs
Electrolyte imbalance	***Electrolyte Imbalance***
Cardiac dysfunction	Effects of cardiopulmonary bypass
Increased systemic vascular resistance	Diuretics
Increased pulmonary vascular resistance	Stress response
Arrhythmias	Fluid administration
Hypothermia	Blood administration
Congestive Heart Failure	Renal failure
Uncorrected CHD (after palliative procedure)	***Neurologic Abnormalities***
Corrected CHD, causing alterations in ventricular preload, contractility, and afterload	Hypoxia
Hypervolemia	Acidosis
Electrolyte imbalance	Poor systemic perfusion
Arrhythmias	Thromboembolism

(*continued*)

TABLE 7.5

COMPLICATIONS OF CARDIAC SURGERY (*continued*)

Respiratory Distress	Electrolyte imbalance
Atelectasis	***Infection***
Pneumothorax	Surgery
Hemothorax	Prosthetic material
Pleural effusion	Invasive monitoring and/or procedures
Chylothorax	Inadequate nutrition
Congestive heart failure	

CHD, congenital heart defect.

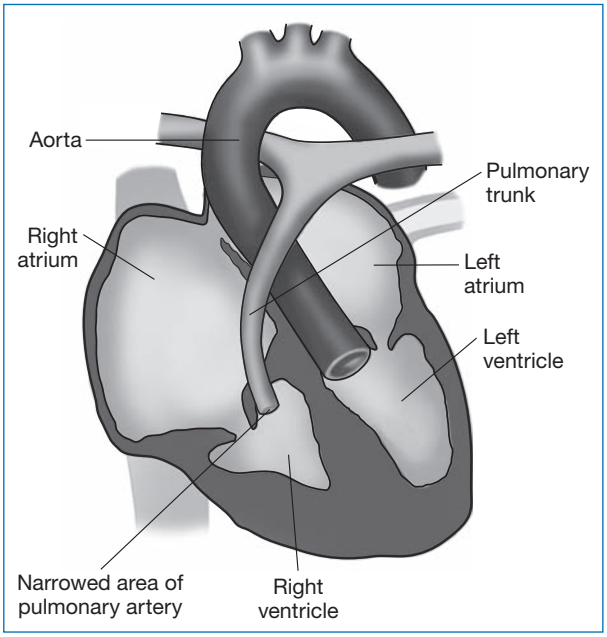

FIGURE 7.10 Pulmonary atresia.

TABLE 7.6

COMPLICATIONS OF CARDIAC SURGERY: POSTOPERATIVE SYNDROMES

	Causes	Manifestations	Treatment
Postcoarctectomy syndrome	Results from changes in pressure and flow	Severe intermittent abdominal pain, fever, and leukocytosis; abdominal distention, melena, and ascites with gangrenous bowel; rebound systemic hypertension	Monitor blood pressure; prevent hypertension; delay postoperative feeding
Postpericardiotomy syndrome	Immunologic syndrome in response to blood in the pericardial sac	Fever, chest pain, pericardial and pleural effusions, hepatomegaly, leukocytosis, left shift, increased ESR, persistent ST and T wave changes on ECG; rare in children younger than 2 years of age	Rest, aspirin for pain, corticosteroids in severe cases, pericardiocentesis if tamponade develops, diuretics
Postperfusion syndrome	Cytomegalovirus	Onset 3–6 weeks after surgery; fever, splenomegaly, atypical lymphocytosis	Supportive care; self-limiting disease process
Hemolytic anemia syndrome	Trauma of RBCs or autoimmune action	Onset 1–2 weeks postoperatively; fever, jaundice, hepatomegaly, reticulocytosis	Iron supplementation or blood transfusions, correction of turbulent flow

ESR, erythrocyte sedimentation rate; RBC, red blood cell.

ventricle palliation pathway with a modified BT shunt in the neonatal period, bidirectional Glenn (BDG), and subsequent Fontan. If the RV is adequate and there are no RV-dependent coronaries, then a two ventricle approach with radiofrequency (RF) perforation of the pulmonary valve along with balloon dilation of the pulmonary valve in the cardiac catheterization laboratory can be undertaken. The presence of a PDA, ASD, or patent foramen ovale (PFO) to allow mixing of blood is crucial for survival (Hanley et al., 1993). PA/IVS is illustrated in Figure 7.10.

Incidence. PA accounts for less than 1% of all CHDs (Park, 2014).

Hemodynamics. PA/IVS manifests as a spectrum of TV and RV hypoplasia. The absence of a RVOT results in high RV end-diastolic pressure, causing tricuspid regurgitation (TR), increasing RA pressure, and causing systemic venous blood to shunt from the RA to the LA through the PFO or ASD. Mixed venous blood flows into the LV and aorta. This is a duct-dependent lesion and the PDA is the only source of pulmonary blood flow. Closure of the PDA causes severe cyanosis, hypoxemia, and acidosis.

Manifestations. PA/IVS results in cyanosis at birth secondary to right-to-left shunt at the atrial level. Tachypnea is present, but there is no obvious respiratory distress. S_2 is single, and TR may produce a harsh regurgitant holosystolic murmur along the lower right and left sternal borders (Park, 2014).

Chest radiograph demonstrates a normal or enlarged heart with a concave main pulmonary artery segment, similar to the appearance of tricuspid atresia. Pulmonary vascular markings are decreased and continue to decrease as the PDA closes.

ECG may reveal a normal QRS axis, left ventricular hypertrophy (type I), or, less frequently, RV hypertrophy (type II), and RA enlargement is seen in approximately 70% of cases (Park, 2014). Echocardiogram demonstrates presence of an atretic pulmonary valve, degree of hypoplasia of the right ventricular cavity and tricuspid valve, amount of tricuspid regurgitation, size of ASD, and possible RV coronary fistula.

Management. Immediate management of PA is administration of prostaglandin to maintain ductal patency. PGE_1 (Prostin) is given as a continuous intravenous infusion. The initial dose varies from 0.025 to 0.1 mcg/kg/minute. When the desired effect is achieved, the dose is incrementally decreased to a maintenance dose of 0.01 mcg/kg/minute. Careful attention to the site of the infusion is important.

Surgical correction versus cardiac catheterization is determined by the size of the tricuspid valve. If the RV is inadequate in size based on a TV annulus *Z* score and/or presence of RV-dependent coronaries, then the neonate will require palliative procedures beginning with a systemic pulmonary artery shunt using Gore-Tex graft tube between the brachiocephalic artery and the pulmonary artery (modified Blalock-Taussig [BT] shunt) in the neonatal period. The surgical mortality rate varies, depending on whether single ventricle palliation or two ventricle repair is required.

Total Anomalous Pulmonary Venous Return

TAPVR is a result of the pulmonary veins draining into the RA (rather than the LA). There are four types of TAPVR (Park, 2014), based on the path of pulmonary venous return: Supracardiac type is the most common and involves drainage of the pulmonary veins via a confluence to the left vertical vein, innominate vein, and right SVC into the RA. Infracardiac type involves pulmonary veins entering a confluence, descending vertical vein that enters the portal vein in the liver to return to the RA via IVC. Cardiac involves drainage to the coronary sinus. Infracardiac is the most common type to be obstructed and typically requires emergent surgery to relieve the obstruction and repair the anomalous pulmonary veins. Mixed type involves a combination of pulmonary venous drainage.

Incidence. TAPVR accounts for 1% of all CHDs. There is a 1:1 male to female ratio of occurrence.

Hemodynamics. TAPVR has an obligate right-to-left shunt at the atrial level to allow some of the oxygenated blood from the anomalous pulmonary venous return that mixes with deoxygenated blood to shunt into the LA to the LV, pumping blood into the aorta and to the systemic circulation.

Two clinical hemodynamic states exist with TAPVR. If pulmonary blood flow is not obstructed, pulmonary flow is greatly increased. The result is highly saturated blood in the RA and mild cyanosis. If there is obstruction to pulmonary blood flow, the volume of flow is decreased, cyanosis is severe, and there is associated pulmonary hypertension. Obstruction to pulmonary blood flow is a common occurrence when the TAPVR is infracardiac (Park, 2014).

Manifestations. The manifestations of TAPVR depend on the presence of pulmonary venous obstruction (PVO). TAPVR without PVO includes a history of mild cyanosis and tachypnea. TAPVR with PVO causes severe cyanosis, respiratory distress, and poor CO (Park, 2014).

Diagnosis. TAPVR without PVO produces a precordial bulge with hyperactive RV impulse. The PMI is at the xiphoid process or LLSB. S_2 is widely split and fixed; the pulmonic sound may be pronounced. A grade 2/6 to 3/6 SEM can be heard at the upper left sternal border, and there is always a middiastolic rumble at the LLSB. The rhythm is a quadruple or quintuple gallop (Park, 2014).

TAPVR with PVO may produce minimal cardiac findings. S_2 is loud and single, and there is a gallop rhythm. There may be a faint SEM at the upper left sternal border. Pulmonary rales may be audible.

Chest radiographic findings of TAPVR without PVO include mild to moderate cardiomegaly and increased pulmonary markings. The characteristic "snowman" sign occurs because of the anatomic appearance of the left SVC, the left innominate vein, and the right SVC. This sign is seldom visible before the patient is 4 months of age. With TAPVR with PVO, the heart size is normal on chest radiograph, and there are signs of pulmonary edema (Park, 2014).

On ECG, TAPVR without PVO has right axis deviation of the QRS axis and sometimes RA enlargement. TAPVR with PVO has right axis deviation for age and RV hypertrophy in the form of tall R waves in the right precordial leads.

Echocardiography of TAPVR demonstrates right-to-left flow across the atrial septum, RA and RV dilation, pulmonary veins draining to a confluence returning to the heart via a vertical vein to the SVC or innominate vein in the supracardiac type, or descending vein to the portal system in infracardiac type. Infracardiac type is the most common to present with obstruction secondary to obstruction of flow that occurs when the descending vein enters the portal system to return to the RA via the DV and IVC. Supracardiac type can also present with obstruction, particularly when blood flow increases to the lungs as the pulmonary vascular resistance decreases. The vertical vein typically passes between the left bronchus and left pulmonary artery and can become compressed by these two structures (Brown & Geva, 2016).

Management. Management of TAPVR is surgical, and surgery is emergent when PVO is infracardiac. Medical management is aimed at preventing or treating CHF and preventing hypoxemia until surgical correction. Diuretics may be required to manage pulmonary edema. Balloon atrial septostomy at cardiac catheterization is performed to enlarge the interatrial communication and promote better mixing of blood. Surgery may be delayed when response to medical management is good, but it is usually performed when the patients are neonates (Park, 2014). The surgical procedure depends on the site of the anomalous drainage. Cardiopulmonary bypass is required. Surgery involves the anastomosis of the pulmonary veins to the LA, closure of the ASD, and division of the anomalous connection. The surgical mortality rate is between 5% and 10% for infants with the unobstructed type. This rate can be as high as 20% for infants with the infracardiac type (Park, 2014).

DEFECTS WITH LV OUTFLOW OBSTRUCTION

These are CHDs resulting from a defect with obstruction to LV outflow, causing reduced or inadequate systemic blood flow. The defects described in this section include aortic stenosis (AS), COA, and HLHS.

Aortic Stenosis

AS is one of a group of defects that produces obstruction to ventricular outflow. AS may be valvular, subvalvular, or supravalvular. Valvular stenosis is the most common, and supravalvular is the least common (Park, 2014).

In valvular stenosis, there is usually a bicuspid valve. Subvalvular stenosis can involve either a subaortic membrane or a long tunnel-like ventricular outflow tract. Idiopathic hypertrophic

subaortic stenosis is a form of subvalvular stenosis that presents as a cardiomyopathy. Supravalvular stenosis is associated with Williams syndrome, or elfin facies, characterized by mental retardation, short palpebral fissures, and thick lips (Park, 2014).

Incidence. AS accounts for 5% of all CHDs. It is four times more common in males.

Hemodynamics. AS causes increased pressure load on the LV, leading to LV hypertrophy. The resistance to blood flow through the stenosis gradually causes a pressure gradient between the ventricle and the aorta, and coronary blood flow decreases. AS is illustrated in Figure 7.11.

Manifestations. Symptoms depend on the severity of the defect. Mild AS is typically asymptomatic; with more severe defects, there is activity intolerance, chest pain, presyncope, or syncope. With severe defects, CHF develops.

Diagnosis. Physical examination reveals normal development without cyanosis. There may be a narrow pulse pressure and a higher systolic pressure in the right arm with severe supravalvular AS. There is a systolic murmur of approximately grade 2/6 to 4/6, best heard at the second right or left intercostal space with transmission to the neck. With valvular AS, there may be an ejection click. With severe AS, there may be paradoxical splitting of S_2. Aortic insufficiency may cause a high-pitched, early diastolic, decrescendo murmur if there is bicuspid aortic valve or subvalvular stenosis (Park, 2014).

Chest radiographs may be normal or may show a dilated ascending aorta, or, in the case of valvular stenosis, a prominent aortic "knob" caused by poststenotic dilation (Park, 2014). Cardiomegaly is present if there is CHF or severe aortic regurgitation. ECG may be normal or may show mild left ventricular hypertrophy and inverted T waves. Echocardiogram may demonstrate a bicuspid aortic valve, dysplastic thickened aortic valve, or in rare cases a unicuspid aortic valve, degree of AS, presence of aortic insufficiency (AI), LVH, and subvalvular and supravalvular AS. Cardiac catheterization may be performed to identify the exact anatomy and to analyze pressure gradients.

Management. Management is aimed at preventing or treating the CHF with fluid restriction, diuretics, and/or digitalis. In children with moderate to severe AS, activity is restricted to prevent increased demand on the heart. Balloon valvuloplasty is sometimes performed at the time of cardiac catheterization to improve circulation. In newborns with critical AS, maintenance of the patency of the DA with PGE_1 at a dose of 0.01 to 0.1 mcg/kg/minute is required to prevent inadequate CO with poor perfusion and metabolic acidosis.

The type of surgical correction depends on the exact location and severity of the defect. The procedure may consist of aortic valve commissurotomy or valve replacement with a prosthetic valve or a graft. The placement of prosthetic valves is usually deferred until adult-sized prosthetic valves can be inserted. The timing of the surgery depends on the severity of the defect. Infants with severe AS without AI will require balloon valvuloplasty and potentially surgery if the gradient does not improve or there is severe AI. Surgery is typically performed on children when there is a peak systolic pressure gradient greater than 50 to 60 mmHg (Park, 2014).

The surgical mortality risk varies depending on the timing and surgical approach required. Surgical mortality for neonates with critical AS is 10% (Park, 2014).

Coarctation of the Aorta

COA is a narrowing or constriction in the aortic arch. The most common location is in the isthmus region located distal to the left subclavian artery. It may be a discrete coarctation or long-segment coarctation associated with aortic arch hypoplasia. COA may occur as a single lesion due to improper development of the aorta, or in rare instances may occur after constriction of the DA. The severity of the circulatory compromise depends on the location and degree of constriction. A large number of infants with COA, more than 75%, have a bicuspid aortic valve (Park, 2014). Coarctation is illustrated in Figure 7.12.

Incidence. COA accounts for 8% of all CHDs. Coarctation occurs twice as often in males. COA is found in 30% of infants with Turner syndrome (Park, 2014).

Hemodynamics. COA causes obstruction to flow that leads to varying pressure across the aortic arch, with the portion of aorta proximal to the constriction with an elevated pressure,

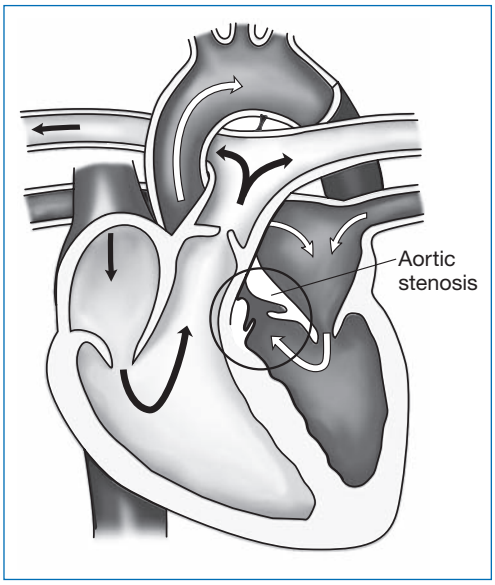

FIGURE 7.11 Aortic stenosis is a narrowing or thickening of the aortic valvular region.

Source: Adapted and modified from Ross Laboratories, Columbus, OH, Clinical Education Aid, 1985.

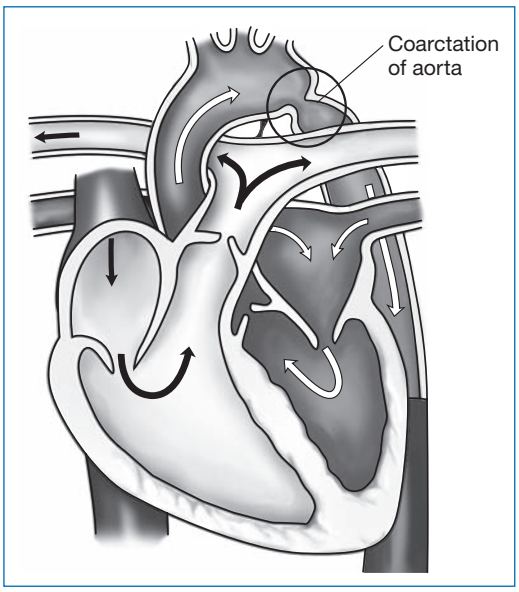

FIGURE 7.12 Coarctation of the aorta is a narrowing or constriction of the aorta near the ductus arteriosus.

Source: Adapted and modified from Ross Laboratories, Columbus, OH, Clinical Education Aid, 1985.

resulting in increased LV pressure. In newborns, right ventricular hypertrophy is a predominant finding since the RV is the main pumping chamber in utero. In cases of delayed diagnosis, the increased LV pressure results in LV hypertrophy and dilation; over time, collateral circulation develops from the proximal to distal arteries, bypassing the constricted segment of the aorta. This is a compensatory mechanism to increase flow to the lower extremities and abdomen resulting in decreased pulses in the lower extremities. COA is shown in Figure 7.11. Children with delayed diagnosis of coarctation will present with elevated systolic blood pressures in the right arm and decreased femoral pulses (Park, 2014).

Manifestations. The severity and time of appearance of symptoms of COA depend on the degree of constriction and associated aortic arch hypoplasia, as well as the presence of associated cardiac defects. COA and/or arch hypoplasia may be missed prenatally (Anuwutnavin et al., 2016). Those neonates with a murmur or who fail pulse oximetry screening for CHD will be diagnosed before becoming symptomatic. Some neonates may go undetected by CCHD pulse oximetry screening, only being diagnosed with coarctation after developing symptoms as the DA closes. In these cases, symptoms of coarctation include CHF with tachypnea, diaphoresis, poor feeding, and weak or delayed pulses in the lower extremities with bounding pulses in the upper extremities. In the presence of CHF, however, all pulses may be weak. With severe COA, S_2 is loud and single, a systolic thrill may be felt in the suprasternal notch, and a SEM of grade 2/6 to 3/6 can be heard at the upper right, middle, or lower left sternal border, and at the left interscapular area on the infant's back; however, no murmur is heard in more than half of infants with COA (Park, 2014).

Diagnosis. Diagnosis of COA is based on history, physical findings, chest radiograph, ECG, and definitive diagnosis by echocardiogram. In asymptomatic infants and children, chest radiographs may show a normal or slightly enlarged heart. In symptomatic infants and children, chest radiographs show cardiomegaly and increased pulmonary venous congestion.

The ECG in asymptomatic children may show left axis deviation of the QRS and LV hypertrophy. In symptomatic children, the ECG reveals normal or right axis deviation of the QRS. RV hypertrophy is present in infants since the RV is the main pumping chamber in utero, whereas LV hypertrophy is present in older children (Park, 2014). Echocardiogram demonstrates the location and degree of the coarctation, presence of aortic arch hypoplasia, and associated defects such as VSD, bicuspid aortic valve, and LV dysfunction.

Management. In neonates prenatally diagnosed with coarctation, a postnatal echocardiogram is performed to assess the severity of coarctation and presence and severity of arch hypoplasia. In some cases, findings from the postnatal echocardiogram will determine postnatal management, with close monitoring for detection of definitive coarctation after the ductus closes versus initiation of PGE_1 to maintain ductal patency until surgical repair. Oxygen saturations in the right hand and right or left foot should be monitored for a significant difference, with saturations in the right or left foot being lower than that in the right hand. The surgical approach depends on the extent of arch obstruction. If there is a discrete coarctation, then surgical repair can be performed via a left thoracotomy. If there is significant arch hypoplasia with coarctation, then a surgical approach via a median sternotomy will be required to augment the arch (Marino, Ostrow, & Cohen, 2006).

The mortality rate for surgical corrections is less than 5% (Park, 2014).

Hypoplastic Left Heart Syndrome

HLHS consists of a group of cardiac defects, including a hypoplastic aortic valve and mitral valve with stenosis or atresia, and a small LA and LV. The great vessels are normally related. There are four different subtypes (mitral atresia with AA, mitral stenosis with AS, mitral atresia with AS, and mitral stenosis with AA). HLHS is illustrated in Figure 7.13.

Incidence. HLHS accounts for 1% to 2% of all CHDs, but it accounts for 7% to 8% of heart defects, producing symptoms in the first year of life; it is the leading cause of death from CHDs in the first month of life (Gilboa et al., 2010).

Hemodynamics. HLHS is a duct-dependent lesion requiring prostaglandin to maintain ductal patency in order to provide systemic blood flow. Since the LV is inadequate or absent, LV output is greatly reduced or absent. Retrograde flow through the aortic arch supplies the head, upper extremities, and coronary arteries. Left atrial and pulmonary venous pressures are elevated, and may result in pulmonary edema.

Although circulation is abnormal in utero, the high pulmonary vascular resistance and the low systemic vascular resistance make survival possible. The RV maintains normal perfusion pressure in the descending aorta by a right-to-left ductal shunt. At birth, the onset of pulmonary ventilation causes decreased pulmonary vascular resistance. The systemic vascular resistance increases because the placenta is eliminated. In cases where HLHS is not prenatally detected, closure of the DA results in decrease in systemic perfusion leading to metabolic acidosis and circulatory shock (Park, 2014).

Manifestations. Neonates with HLHS may be asymptomatic and have near-normal saturations if there is an adequate atrial communication and mixing of blue and pink blood. Importantly, these neonates may not be detected by CCHD pulse oximetry screening typically performed at 24 hours of age since the ducts may be patent. As the ductus closes, circulatory shock develops resulting in metabolic acidosis with signs and symptoms of progressive cyanosis, tachypnea, tachycardia, and poor peripheral pulses. Typically, the S_2 is single and a cardiac murmur may be

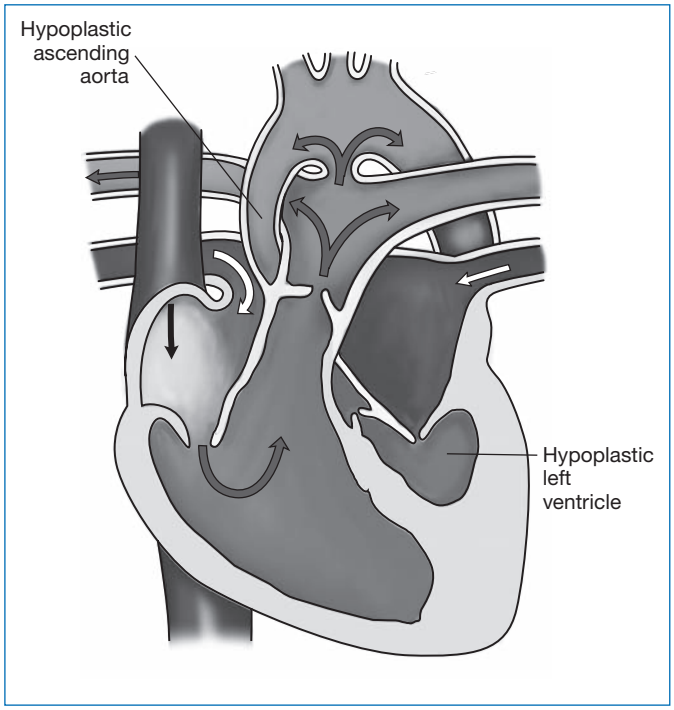

FIGURE 7.13 Hypoplastic left heart syndrome.

absent in neonates with mitral and aortic atresia. In neonates with mitral stenosis and AS, there may be a grade 2/6 to 3/6 systolic murmur (Park, 2014).

Diagnosis. Chest radiograph of HLHS demonstrates mild to moderate heart enlargement and pulmonary venous congestion or pulmonary edema. RV hypertrophy is the characteristic finding on ECG. Echocardiography is diagnostic demonstrating hypoplastic or even absent left-sided heart structures. There may be mitral or aortic stenosis or mitral or aortic atresia associated with a hypoplastic LA, LV, and ascending aorta/aortic arch, RV dilation, and hypertrophy. Size of the ASD and presence of tricuspid regurgitation should also be documented.

Management. Medical management of HLHS is aimed at maintaining ductal patency through continuous infusion of PGE_1 to prevent significant hypoxemia and metabolic acidosis. In rare cases of a restrictive atrial septum, balloon atrial septostomy and/or stenting of the atrial septum may be required if there is an inadequate atrial communication.

Surgical palliation of HLHS is complex and has a high mortality rate; however, over 30 years ago, HLHS was once considered 100% fatal. The goal of surgical palliation is to separate the deoxygenated and oxygenated blood in three stages. The first-stage procedure, the modified Norwood procedure, is typically performed in the first week of life. The Stage I/Norwood procedure involves building a neoaorta utilizing the main pulmonary artery and a BT shunt (Gore-Tex graft tube) or a Sano (RV-PA conduit tube) to provide stable pulmonary blood flow with an atrial septectomy to create adequate atrial communication. Infants with a Stage I/Norwood typically have oxygen saturations of 75% to 80%. The second-stage procedure, the BDG, is typically performed at 4 to 6 months of age. The BDG involves dividing the SVC and anastomosing it to the RPA along with ligating the BT shunt. Infants with BDG have saturations of 80% to 85%. The third-stage procedure, a modified Fontan procedure, is typically performed at 2 years of age. The modified Fontan procedure involves dividing and anastomosing the IVC to the RPA. Children with a Fontan have normal oxygen saturations unless they have a fenestrated Fontan. In some patients who are higher risk for a Fontan or in some centers, the Fontan is fenestrated and these patients will have lower saturations until the fenestration spontaneously closes or is closed later via transcatheter device closure (Goff et al., 2000; Marino et al., 2006).

See Table 7.7 for a description of these procedures (Park, 2014).

The aggregate surgical mortality rate for the Stage I/Norwood palliation procedure, which includes HLHS, is 15.8%. If patients survive up to the BDG/hemi-Fontan and Fontan procedure, the aggregate surgical mortality rate decreases to 2.1% and 1.1%, respectively (Jacobs et al., 2018).

Nursing care focuses on assessment of CO, systemic perfusion, and adequate pulmonary blood flow during the immediate postoperative period. Postoperative care requires close monitoring of vital signs, chest tube output, urine output, laboratory values (hemoglobin, platelets, BUN/Cr, AST/ALT), and pulmonary and circulatory status. Attention to nutritional status is important for long-term recovery.

Dopamine at 5 mcg/kg/minute may be needed to augment CO along with milrinone 0.5 to 1 mcg/kg/minute. Diuretics and/or peritoneal dialysis may be necessary to maintain fluid balance. Fentanyl and Versed drips may be used for sedation and analgesia. In many institutions, Stage I/Norwood patients return to the cardiac intensive care unit (CICU) on extracorporeal membrane oxygenation (ECMO) to maintain oxygenation and CO during the immediate postoperative period, whereas many other institutions maintain an open chest for several days to allow optimization of CO and ventilation (Marino et al., 2006).

Nutritional support is provided through total parenteral nutrition (TPN). Monitoring of daily weights, of urine for ketones, glucose, and protein, and of serum levels of electrolytes and trace minerals is necessary to adjust the parenteral fluids. Enteral feedings may be started in the first few weeks postoperatively once the neonate has been deintensified, is hemodynamically stable, and where NEC risk is somewhat decreased.

Although an alternative treatment approach for HLHS is cardiac transplantation, the wait time for heart transplant in infants is on average 4 to 6 months in many regions; so, listing for heart transplant is primarily utilized for those neonates with poor RV function who are not good candidates for the Stage I/Norwood procedure. Further information about cardiac transplantation is found in Chapter 27, Newborn or Infant Transplant Patient. It is essential that parents be counseled and informed of all available treatment options, including risks and short- and long-term prognoses. Improvement in overall survival has led to an increased focus on long-term morbidity, particularly neurobehavioral and neurocognitive issues. ND problems are common in this cohort and are further discussed in the section on age-related ND problems (Marino et al., 2012).

DEFECTS WITH ABNORMAL AORTOPULMONARY CONNECTIONS

These CHDs result from a developmental defect of either the vascular or the valvular system, frequently with cyanosis. The defects described in this section include TGA and truncus arteriosus.

Transposition of the Great Arteries or Vessels

TGA is the result of abnormal rotation of the outflow tracts during fetal cardiac development. TGA may be dextrotransposition of the great arteries (*d*-TGA) or levotransposition of the great arteries (*L*-GA). In *d*-TGA, the aorta arises from the RV and the pulmonary artery arises from the LV. The aorta receives deoxygenated systemic venous blood and returns it to the systemic arterial circuit. The pulmonary artery receives oxygenated pulmonary venous blood and returns it to the pulmonary circulation. *d*-TGA is illustrated in Figure 7.14.

In *L*-TGA, both the ventricles and the great vessels are transposed, with the aorta arising from the left-sided RV and the pulmonary artery arising from the right-sided LV. The aorta is to the left and anterior to the pulmonary artery. This type of transposition is called *corrected*, because physiologically the cardiac hemodynamics are normal except that the RV is the systemic pumping chamber. The oxygenated blood comes into the LA, enters the left-sided RV, and is pumped via the aorta to the systemic circulation. Frequently, there are other associated cardiac defects; but in the absence of these defects, *L*-TGA may go undetected until a patient reaches adulthood and develops RV heart failure adult congenital heart disease (ACHD); Park, 2014).

Incidence. *d*-TGA accounts for 5% of all CHDs. It is more common in males (3:1). *d*-TGA is the most common cyanotic heart defect in newborns.

Hemodynamics. Hemodynamically, *d*-TGA results in parallel circulation. Oxygenated blood from the lungs is returned to the LA and enters the LV, which pumps blood back to the lungs via the pulmonary artery. Deoxygenated blood from the systemic veins returns to the RA and enters the RV, which pumps blood into the systemic circulation via the aorta. The end result is that the heart, brain, and other vital tissues are perfused with deoxygenated blood. **Emergency Alert: This**

TABLE 7.7

COMMON CARDIAC SURGICAL PROCEDURES

Procedure	Type	Defect	Description
Modified BT shunt	Palliative	Single ventricle with PA, TOF/PA, PA/IVS	Synthetic tube from the brachiocephalic artery to the pulmonary artery to provide a stable source of pulmonary blood flow
Stage I Procedure Norwood/ Damus-Kaye-Stansel	Palliative	HLHS/HLH variants	1. Main pulmonary artery is divided, and anastomosed to the hypoplastic ascending aorta to provide unobstructed systemic and coronary blood flow 2. Modified BT shunt to provide a stable source of pulmonary blood flow 3. Atrial septectomy to allow interatrial mixing
Superior caval connection (Bidirectional Glenn)	Palliative	Single ventricles	1. SVC anastomosis to the RPA 2. Ligation and division of the BT shunt
Modified Fontan	Palliative	Single ventricles	Lateral tunnel (inferior baffle from IVC to SVC) or extracardiac conduit (Gore-Tex tube connection between the vena cava)
Rashkind	Corrective	TGA, HLHS restrictive atrial septum	Balloon atrial septostomy to enlarge the atrial communication
Jatene/ Arterial switch procedure	Corrective	TGA	Switching of TGA to their anatomically correct position along with reimplantation of coronary arteries into the neoaorta
Rastelli	Corrective	TGA, TOF, PA, truncus arteriosus	Commonly applied to all valved conduits from the right ventricle to pulmonary artery
Pulmonary artery banding	Palliative	Multiple VSDs, single ventricles with unobstructed outflow	Placement of a band around the pulmonary artery to decrease the blood flow to the lungs

ASD, atrial septal defect; BT, Blalock-Taussig; HLHS, hypoplastic left heart syndrome; IVC, inferior vena cava; IVS, intact ventricular septum; PA, pulmonary artery; PVA, pulmonic valve atresia; PS, pulmonary stenosis; PV, pulmonary valve; RPA, right pulmonary artery; SVC, superior vena cava; TA, truncus arteriosus; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

Sources: Data from Marino, B. S., Ostrow, A. M., & Cohen, M. S. (2006). Surgery for congenital heart disease. In V. Vetter (Ed.), *Pediatric cardiology: The requisites in pediatrics* (pp. 277–320). Philadelphia, PA. Mosby Elsevier; Park, M. K. (2014). *Pediatric cardiology for practitioners.* Chicago, IL: Mosby.

defect is incompatible with life unless there is an adequate atrial communication to allow mixing of the oxygenated and deoxygenated blood. Some cases of *d*-TGA have associated VSDs, which may contribute a little to mixing of oxygenated and deoxygenated blood, but the ASD is required for adequate mixing of blood (Park, 2014).

Manifestations. In cases detected prenatally, PGE_1 is initiated after birth and arterial blood gases (ABGs) are monitored for significant hypoxia in cases not detected prenatally. Cyanosis is typical and may be severe if the atrial communication is restrictive. The right upper saturation typically is lower than the right or left lower leg oxygen saturation, particularly if the atrial communication is restricted (Rudolph, 2001).

Diagnosis. Chest radiograph of *d*-TGA demonstrates a classical finding of an egg-shaped heart, where the heart is enlarged with a narrow base because the aorta is anterior to the pulmonary artery (Park, 2014). On ECG, there is right axis deviation of the QRS and RV hypertrophy. Echocardiography is important to evaluate the adequacy of the atrial communication, presence and size of VSDs, aortic or pulmonary valve abnormalities, and coarctation. In addition, the coronary pattern is important because a small percentage of coronary patterns will require an alternative surgical approach in rare cases.

Management. *d*-TGA may be a cardiac emergency in those neonates who are not prenatally detected and have a restrictive atrial septum. Immediate medical management includes initiation of PGE_1; correction of acidosis, hypoglycemia, hypocalcemia; administration of oxygen; and access to emergent balloon atrial septostomy to promote mixing of oxygenated and deoxygenated blood at the atrial level (Park, 2014).

Surgical correction involves the Jatene or arterial switch operation (ASO), which involves switching the arteries and coronaries (Jatene procedure) along with bringing the branch pulmonary arteries across the anterior aspect of the aorta (LeCompte). See Table 7.7 for a description of these procedures.

Outcomes after the ASO are quite good with aggregate mortality rates of 2.7% for *d*-TGA without a VSD and 5.3% for *d*-TGA with VSD (Jacobs et al., 2018). In the long term, these patients may develop problems with branch pulmonary arteries and coronary problems. Children with *d*-TGA status post ASO have been one of the most widely studied groups for ND problems (Marino et al., 2012).

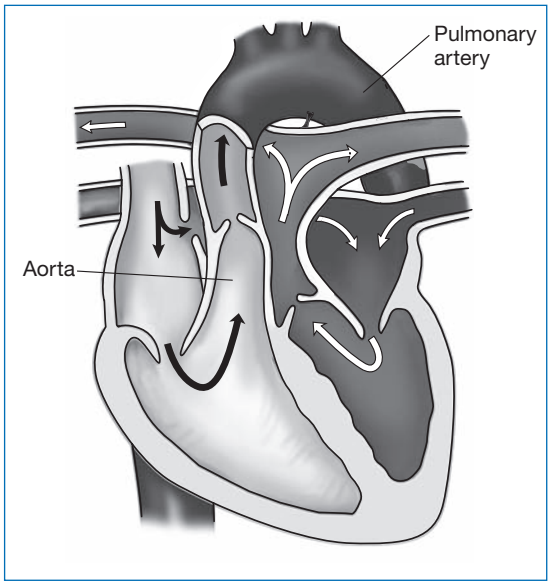

FIGURE 7.14 Transposition of the great arteries or vessels is a condition in which the aorta arises from the right ventricle and the pulmonary artery arises from the left ventricle. The result is two distinct circulatory (parallel) pathways.

TABLE 7.8

FOUR MAJOR TYPES OF TRUNCUS ARTERIOSUS

Type	Incidence (%)	Description
I	60	Main pulmonary artery arises from truncus and divides into left and right pulmonary artery; results in increased pulmonary blood flow
II	20	Pulmonary artery arises from posterior portion of truncus arteriosus; pulmonary blood flow is normal or increased
III	10	Pulmonary artery arises from sides of truncus arteriosus; pulmonary blood flow is normal or increased
IV	10	Bronchial arteries arise from descending aorta to supply lungs; pulmonary blood flow may be decreased

Truncus Arteriosus

Early fetal development involves a single, large great vessel or trunk arising from the ventricles, which ultimately gives rise to the systemic and pulmonary circulations. During development, if there is inadequate septation of the trunk then both the pulmonary and aortic outflows will arise from one large vessel, and inadequate septation of the ventricular septum will result in a large VSD. Four types of truncus arteriosus have been described; see Table 7.8 for the classifications (Park, 2014). Truncus arteriosus is illustrated in Figure 7.15.

Incidence. Truncus arteriosus accounts for less than 1% of all CHDs.

Hemodynamics. Deoxygenated blood from the RV and oxygenated blood from the LV mix via the large VSD and enter the truncal artery. The pressures of both ventricles are equal as a result of the large VSD. The amount of flow to the pulmonary and systemic circulations depends on the resistance of the two circulations. Pulmonary vascular resistance is high at birth, so pulmonary and systemic flows are relatively equal initially. Pulmonary resistance gradually decreases, causing increased pulmonary blood flow. CHF may develop as a result of increased pulmonary blood flow and there may be associated inadequate systemic perfusion. If not corrected early, over time, pulmonary vascular disease develops in response to increased pulmonary blood flow; subsequently, pulmonary blood flow decreases as a result of development of increased pulmonary vascular resistance. These changes, although compensatory initially, complicate the hemodynamics with increased risk for pulmonary hypertension in the postoperative period. The volume overload can also be compounded by incompetent truncal valves that allow regurgitation of blood into the ventricles.

Manifestations. If truncus arteriosus is not prenatally diagnosed, it typically will be detected in the newborn period as a result of a murmur, cyanosis, symptoms of poor feeding, and signs of CHF; or it may be detected on CCHD pulse oximetry screening. The presence of cyanosis depends on the amount of pulmonary blood flow, and signs of CHF due to increased pulmonary blood flow may be the first indication of truncus arteriosus. On auscultation,

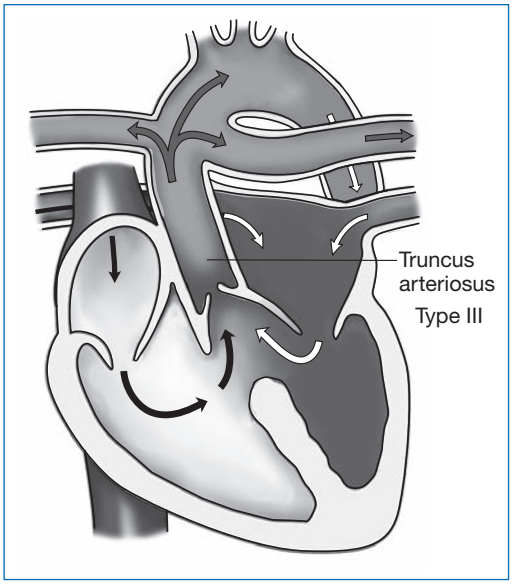

FIGURE 7.15 The truncus arteriosus is a single arterial vessel that gives rise to the coronary arteries, pulmonary arteries, and aorta.

Source: Adapted and modified from Ross Laboratories, Columbus, OH, Clinical Education Aid, 1985.

S_2 is single and there may be a systolic click at the apex and upper left sternal border. A murmur may be auscultated if there is truncal stenosis or insufficiency. Truncal valve insufficiency produces a high-pitched, early diastolic decrescendo murmur. There may be bounding arterial pulses and a widened pulse pressure. The right upper oxygen saturation and lower right and left oxygen saturations will be similar and less than 95%.

Diagnosis. On chest radiograph, the heart size is increased and pulmonary blood flow may be increased. Thirty-five percent of cases have a right aortic arch, and this finding increases the risk of deletion of 22q11. ECG reveals a normal QRS axis and ventricular hypertrophy. Echocardiography demonstrates the presence of a

single common arterial truncal valve overriding a large VSD and further details of the type of truncus with location of the pulmonary arteries, presence of truncal stenosis/insufficiency, additional VSDs, and arch sidedness (Park, 2014; Schultz & Kreutzer, 2006).

Management. Medical management consists primarily of treatment of CHF. Current surgical correction consists of complete primary repair, with closure of the VSD, committing the common arterial trunk to the LV, and reconstruction of the RVOT with a conduit from the RV to the branch pulmonary arteries (Park, 2014). The definitive surgical correction is the Rastelli procedure (see Table 7.7 for a description of common surgical procedures). Surgery is typically performed in the first week of life. The aggregate surgical mortality rate for truncus is 10.1%. Repeat surgery typically is required to enlarge the conduit as growth occurs (Jacobs et al., 2018; Park, 2014).

Congenital Arrhythmias

Cardiac arrhythmias in infants generally arise from primary cardiac lesions as a result of abnormal conduction pathways. Alternatively, cardiac arrhythmias can develop following cardiac surgical palliation or repair. It is not clear whether the arrhythmia is secondary to the cardiac lesion or the surgical procedure. Some arrhythmias are a result of electrolyte imbalances, neurologic conditions, or infections. Generally, in infants, rhythm disturbances are not the primary manifestation of a cardiac problem; instead, CHF or cyanosis is present before dysrhythmias occur (Sacchetti, Moyer, Baricella, Cameron, & Moakes, 1999). Some conditions present with rhythm disturbances in the newborn period. The most commonly occurring include congenital complete heart block (CCHB) and supraventricular tachycardia (SVT). These two arrhythmias are discussed in more detail.

Congenital Complete Heart Block

The AV node and the bundle of His arise as separate structures that join. CCHB is a result of a discontinuity between the atrial conduction pathway and the AV node, or the bundle of His and the AV node. One risk factor for CCHB is exposure to SSA and SSB antibodies in utero due to maternal systemic lupus erythematosus (SLE). In most cases, the heart structure is normal and the etiology of CCHB is unknown. Congenital heart block can also be a manifestation of CHDs, including congenitally corrected TGA or *L*-TGA.

Prenatally, CCHB can be detected by fetal bradycardia (HR < 100 bpm) on auscultation, electronic monitoring, or screening ultrasound. Fetal echocardiography is diagnostic with identification of AV dissociation with atrial rate faster and not associated with the slower ventricular rate by M-mode, and spectral Doppler techniques of the inflow and outflow of the heart (O'Connor & Shah, 2012).

Treatment. Asymptomatic neonates do not require treatment. If the neonate has inadequate systemic perfusion due to the bradycardia, then insertion of a pacemaker may be required. Children with implanted pacemakers need close follow-up due to complications or adverse effects of the pacemakers (Massimo et al., 2006; Webb et al., 2012).

Supraventricular Tachycardia

SVT can arise in utero or in the neonatal period. The most common arrhythmias that produce signs are paroxysmal SVT with or without ventricular preexcitation, atrial flutter, and junctional tachycardia. If the SVT occurs in utero, it can lead to heart failure and hydrops fetalis. SVT treatment depends on gestational age of the fetus, the type of SVT, whether it is intermittent or persistent, and the presence of CHF and/or hydrops. SVT treatment in the fetus depends on the presence or absence of hydrops. If the fetus is near term, then delivery with postnatal treatment may be the management strategy. If the patient is not near term, then the medication regimen depends on the type of SVT and presence or absence of hydrops. In paroxysmal SVT without hydrops, digoxin, flecainide, or sotalol may be used as first-line therapy. If first-line therapy is not successful, then combination therapy will be used (O'Connor & Shah, 2012).

In most cases of SVT, no cause is found. Ebstein anomaly of the tricuspid valve can be the cause in some cases. Ten to 50% of infants with SVT have Wolf-Parkinson-White (WPW) syndrome, in which the atrial impulse activates the whole or some part of the ventricle, or the ventricular impulse activates the whole or some part of the atrium earlier than would be expected if the impulse traveled via the normal pathway. WPW is characterized by a normal QRS with regular rhythm and ventricular rates of 150 to 200 bpm (Olgin & Zipes, 2011).

Symptoms produced by SVT after birth are subtle and often undetected until signs of CHF develop. Medical management typically begins with vagal maneuvers; elicitation of a diving reflex by covering the face with a cold washcloth for 4 to 5 seconds is generally successful in establishing normal sinus rhythm. If this approach is unsuccessful, then IV adenosine is attempted, typically resulting in cardioversion to sinus rhythm. A baseline 12-lead EKG is required to document presence of delta waves consistent with WPW, since it will determine the medical management and medication therapy used. Propranolol is a common medical therapy used, particularly if WPW is diagnosed. In some centers, digoxin therapy may be utilized for SVT when WPW has been ruled out. Infants are followed closely for breakthrough SVT episodes; if no further SVT is documented, then at 1 year of age medical therapy is discontinued with close follow-up to monitor for SVT recurrence. Since recurrence is more likely in WPW, these infants typically will be maintained on beta blocker therapy.

Recurrence decreases between ages 2 and 10 years of age. Prognosis for SVT is good (Webb et al., 2012).

Congestive Heart Failure

Congestive heart failure (CHF) is a condition in which the blood supply to the body is insufficient to meet the metabolic requirements of the organs. CHF is a manifestation of an underlying disease or defect, rather than a disease itself. Before development of CHF, compensatory mechanisms are activated to maintain adequate CO (Park, 2014; Wernovsky & Gruber, 2005). Normal mechanisms for regulation of CO are listed in Box 7.2. CHF is classified according to the cause. Box 7.3 shows common causes of CHF in newborns.

Increased volume may be caused by fluid overload or fluid retention. In the normally functioning myocardium, fluid retention does not cause CHF; however, fluid retention complicates CHF from other causes. In neonates, the most common cause of increased volume is CHD or altered hemodynamics, as in PDA.

CHF caused by obstruction to outflow occurs when the normal myocardium pumps against increased resistance. This increased resistance may be caused by structural defects, such as valvular stenosis or COA, or by pulmonary disease and/or pulmonary hypertension. CHF caused by pulmonary disease is called *cor pulmonale*. Severe systemic hypertension can also cause increased systemic vascular resistance.

CHF in the neonate usually results from abnormal stresses placed on the heart rather than from an ineffective myocardium. However, electrolyte imbalances, acidosis, and myocardial ischemia affect the ability of the heart to function effectively. Conditions such as rheumatic fever, infectious myocarditis, Kawasaki

Box 7.2

MECHANISMS OF CARDIAC OUTPUT REGULATION

Sympathetic Nervous System Activated By:

- Vasomotor center through peripheral sympathetic fibers
- Secretion of norepinephrine from adrenal medullary "fight or flight" response
- Symptoms
  - Characterized by tachycardia, increased contractility, peripheral vasoconstriction, pupil dilation

Parasympathetic Nervous System Activated By:

- Vagal fibers
  - Atrial stimulation causes decreased heart rate.
  - Ventricular stimulation causes decreased contractility.
- Baroreceptor reflexes
  - Located in walls of carotid sinuses and in aortic arch
  - Pressure receptors stimulated by blood pressure
- Results
  - Stimulation causes inhibition of the sympathetic portion of the vasomotor center and stimulation of the parasympathetic (vagal) center; decreased arterial blood pressure

Box 7.3

CAUSES OF CONGESTIVE HEART FAILURE IN THE NEWBORN

Noncardiac causes of congestive heart failure:

- Sepsis
- Anemia
- Polycythemia
- Metabolic diseases (Pompe disease)
- Multiple hemangiomas
- Arteriovenous malformations (cranial, hepatic, abdominal)
- Hyperthyroidism
- Hypoglycemia
- Hypocalcemia
- Renal failure
- Severe systemic hypertension

Congenital heart defects:

- Hypoplastic left heart syndrome
- Interrupted aortic arch
- Coarctation of the aorta
- Total anomalous pulmonary venous return with obstruction
- Transposition of the great arteries
- Patent ductus arteriosus (in preterm infants)

Other cardiac causes:

- Myocarditis
- Arrhythmias
- Anomalous left coronary artery from the pulmonary artery

disease with myocarditis, and anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA) may reduce the effectiveness of the heart function.

Arrhythmias that may produce CHF include complete AV block or sustained atrial or ventricular tachycardia. AV block results in a severe bradycardia that prohibits adequate circulation of blood. Tachycardia causes insufficient time for ventricular filling, decreasing CO and leading to cardiac dysfunction over time.

Severe anemia can cause CHF because of excessive demand for CO. Because the oxygen-carrying capacity of the blood is diminished, the heart must pump more blood per minute to meet the tissue oxygenation requirements. If the heart cannot meet the excessive demand, CHF develops (Park, 2014).

Compensatory mechanisms function to meet the body's increased demand for CO. These mechanisms are regulated by the sympathetic nervous system and mechanical factors. The compensatory mechanisms can sustain adequate CO for only a short period of time. If the underlying condition is not corrected, CHF develops.

Sympathetic Nervous System Compensatory Mechanisms. Decreased blood pressure stimulates vascular stretch receptors and baroreceptors in the aorta and carotid arteries that trigger the sympathetic nervous system. Decreased systemic blood pressure stimulates baroreceptors, causing (1) increased sympathetic stimulation, (2) increased HR, (3) increased cardiac contractility, and (4) increased arterial blood pressure. Catecholamine release and beta-receptor stimulation increase the rate and force of myocardial contraction. Catecholamines also increase venous tone, so that blood is returned to the heart more effectively. Circulation to the skin, kidneys, extremities, and splanchnic bed is decreased, allowing better circulation to the brain, heart, and lungs. Decreased renal blood flow stimulates the release of renin, angiotensin, and aldosterone. This release causes retention of sodium and fluid, resulting in increased circulating volume. The increased volume puts additional work on the heart.

Mechanical Compensatory Mechanisms. The heart muscle thickens to increase myocardial pressure. The hypertrophy is effective in the early stages, but as soon as the muscle mass increases, compliance decreases. This change in compliance requires greater filling pressure to maintain adequate CO. The hypertrophied heart eventually becomes ischemic because it does not receive adequate oxygenation to meet its metabolic needs. Ventricular dilation occurs as myocardial fibers stretch to accommodate heart volume. Initially, this increases the force of the contraction, but it too fails after a certain threshold point.

Effects of Congestive Heart Failure. When the RV is unable to pump blood into the pulmonary artery, the lungs oxygenate less blood, there is increased pressure in the RA and systemic venous circulation, and edema occurs in the extremities and viscera. When the LV is unable to pump blood into the systemic circulation, there is increased pressure in the LA and pulmonary veins. The lungs become congested with blood, causing elevated pulmonary pressures and pulmonary edema.

The end effects of CHF include decreased CO, decreased renal perfusion, systemic venous engorgement, and pulmonary venous engorgement and their consequent effects. Decreased CO stimulates the sympathetic nervous system, causing tachycardia, increased contractility, increased vasomotor tone, peripheral

vasoconstriction, and diaphoresis. Decreased renal perfusion stimulates the renin-angiotensin-aldosterone mechanism, causing sodium and water retention. Systemic venous engorgement leads to hepatomegaly, jugular venous distention, periorbital and facial edema, and, occasionally, ascites and dependent edema. Pulmonary venous engorgement results in tachypnea, decreased tidal volume, decreased lung compliance, increased airway resistance, early closure of the small airways with air trapping, increased work of breathing, and increased respiratory effort, grunting, and rales. Stimulation of the j-receptors in the lung causes infants to become apprehensive and irritable.

Diagnosis. The diagnosis of CHF is based on clinical signs and symptoms, laboratory data, and chest radiography with definitive diagnosis by echocardiography. In contrast to infants with cyanotic heart disease, infants with CHF usually have significant respiratory distress with tachypnea, grunting, and retractions. They exhibit peripheral pallor, appearing to be ashen or gray in color. The precordium is hyperdynamic, and there are usually loud murmurs heard throughout systole and diastole. Pulses are usually full, but there may be a difference between the upper and the lower extremities. Hepatomegaly is common. Infants demonstrate signs of irritability because of the increased effort of breathing and air hunger.

In addition to demonstrating hypoxemia, ABG may reveal a metabolic acidosis resulting from the decreased systemic blood flow. If acidosis is severe, there may be concurrent respiratory acidosis because of the pulmonary edema caused by left-sided heart failure. Pulmonary ventilation–perfusion mismatch may cause hypoxemia. Hypocalcemia is often present in infants with CHF because they have an inappropriate response to stress. In addition, infants with deletion of 22q11 may have hypocalcemia because of absent parathyroids. Conotruncal anomalies such as TOF and truncus arteriosus along with interrupted aortic arch are CHDs that are commonly associated with deletion of 22q11 (Park, 2014).

Hypoglycemia may be present in infants with severe CHF. The myocardium depends on glucose; decreased glucose levels diminish the ability of the heart to compensate for CHF. On chest radiograph, the heart is enlarged and there is increased pulmonary congestion. ECG is not generally diagnostic, unless the CHF is caused by an arrhythmia. There may be nonspecific changes in the T waves, changes in the ST segment, and an increase in the height of the P wave.

Electrolyte imbalances usually include relative hyponatremia due to increased free water. Hypochloremia and increased bicarbonate may result from respiratory acidemia and the use of loop diuretics. Hyperkalemia results from the release of intracellular cations related to poor tissue perfusion. Elevated lactic acid levels are also indicative of tissue hypoxia. Atrial natriuretic factor (ANF), a peptide hormone, may be important in the regulation of volume and blood pressure. ANF is released from the atria when they are distended. ANF release causes natriuresis, diuresis, and vasodilation. ANF acts with other volume regulators, such as renin, aldosterone, and vasopressin. An increased ANF level may be found when there is increased pulmonary blood flow, increased left atrial pressure, or pulmonary hypertension.

Treatment. The goal of management of CHF is to improve cardiac function while identifying and correcting the underlying cause. General measures that decrease the demand on the heart are helpful; however, pharmacologic intervention is the most efficacious therapy.

General Measures. General measures to manage CHF in infants with structurally normal hearts include the administration of oxygen to improve ventilation and perfusion at the alveolar level. Ventilation with positive end-expiratory pressure at 6 to 10 cm/H_2O may relieve the effects of CHF by reducing pulmonary edema.

Fluid restriction may decrease the circulating volume. Careful monitoring of serum electrolytes, BUN/Cr, intake and output, and weight is essential. It is imperative that *all* fluids be counted in the total daily fluid volume. Infants with CHF do not usually feed well and may require caloric supplementation with hyperalimentation or gavage feedings (Park, 2014).

Infants with CHF are irritable and agitated, further complicating their hemodynamic status. Sedation with continuous infusions of morphine sulfate or fentanyl may improve the infant's comfort level and oxygenation by decreasing metabolic demand. Other measures that reduce metabolic oxygen demand include maintenance of a normal hematocrit, maintenance of a thermoneutral environment, and minimal stimulation (Verklan & Walden, 2004).

Pharmacologic Interventions. Table 7.9 lists the medications most commonly used in the management of cardiac conditions. Medical management of CHF *beyond* the neonatal period includes use of ACE inhibitors, diuretics, nonspecific beta blockers (carvedilol), and/or digitalis (digoxin). Digoxin slows conduction through the AV node, prolongs the refractory period, and slows the HR through vagal effects on the SA node.

The use of digoxin in preterm or term neonates is controversial. The preterm newborn is at risk for digitalis toxicity because of the narrow range between therapeutic and toxic drug levels. The preterm infant requires a lower maintenance dose because of limited renal excretion of the drug (Table 7.10). If digoxin is used, the neonate must be carefully monitored for signs and symptoms of digitalis toxicity. Lead II ECGs should be obtained before each dose for the first 3 days; the dose should be withheld if the PR interval is greater than 0.16 second or if there is an arrhythmia present. Digoxin levels should be monitored and should be less than 2.0 ng/mL (Park, 2014). Blood samples for digoxin levels should be drawn after the drug has achieved equilibrium in the body, approximately 6 to 8 hours after administration.

Other inotropic agents can be used to improve CO. Dopamine, a norepinephrine precursor, has direct and indirect dose-dependent beta adrenergic effects. At low doses (2–5 mcg/kg/minute), there is increased renal blood flow with minimal effect on HR, blood pressure, or contractility. Medium doses (5–10 mcg/kg/minute) increase renal blood flow, HR, blood pressure, and contractility. Pulmonary artery pressure may be increased; peripheral resistance is not affected. High doses (10–20 mcg/kg/minute) cause peripheral vasoconstriction, increased cardiac rate, and increased contractility (Park, 2014).

Dobutamine is a synthetic catecholamine that acts on beta and alpha adrenergic receptors. Dobutamine (2–10 mcg/minute) has decreased effect on the HR and rhythm and causes less peripheral vasoconstriction.

Emergency Alert: Isoproterenol (Isuprel), a synthetic epinephrine-like substance, has beta-1 and beta-2 adrenergic effects. The usefulness of Isuprel in the neonate is limited because it produces increased HR, arrhythmias, and decreased systemic vascular resistance, which may worsen the hypotension (Park, 2014).

Diuretics. Diuretics are useful in the treatment of CHF to decrease sodium and water retention. The primary goal is to increase renal perfusion (with inotropic agents or vasodilators) and to increase sodium delivery to distal diluting sites of the renal tubules. Diuretic agents increase the renal excretion of sodium and other anions by inhibition of tubular reabsorption of sodium (Park, 2014).

Furosemide (Lasix), a loop diuretic, blocks sodium and chloride reabsorption in the ascending limb of the loop of Henle. Loop

TABLE 7.9

DRUGS USED IN THE MANAGEMENT OF CONGENITAL HEART DEFECTS

Drug	Dosage	Action	Onset	Comments
Diuretics				
Furosemide (Lasix)	0.5–1 mg/kg/dose IV	Loop diuretic; inhibits sodium and chloride reabsorption in proximal tubule	15–30 minutes	Associated with increased calcium loss
Furosemide (Lasix)	1–3 mg/kg/dose PO		30–60 minutes	
Spironolactone (Aldactone)	1.5–3.0 mg/kg/dose PO	Competitive antagonist of aldosterone	3–5 days	Potassium sparing
Chlorothiazide	20–40 mg/kg/day PO	Inhibits sodium and chloride reabsorption along the distal tubules	1–2 hours	
Inotropic Agents				
Dopamine	Low: 2–5 mcg/kg/minute	Increased renal blood flow; beta adrenergic effects		Monitor ECG; BP
	Mod: 5–10 mcg/kg/minute	Increased renal blood flow; heart rate, BP, and contractility		
	High: 10–20 mcg/kg/minute	Peripheral vasoconstriction, increased heart rate, and contractility		
Dobutamine	2–10 mcg/kg/minute	Increased renal blood flow; increased contractility	Rapid	Decreased systemic vascular resistance; increased pulmonary wedge pressure
Isoproterenol	0.05–0.5 mg/kg/minute	Increased venous return to heart and decreased pulmonary vascular resistance		Tachycardia, dysrhythmias, decreased renal perfusion
Prostaglandins				
PGE_1	0.01–0.1 mg/kg/minute	Produces vasodilation and smooth muscle relaxation of ductus arteriosus and pulmonary and systemic circulations; increased arterial saturation by 25%–100%	Rapid	Monitor BP; vasopressors may be required; apnea, flush, fever, seizure-like activity; decreased heart rate
Prostaglandin Synthetase Inhibitors				
Indomethacin	0.2 mg/kg IV (1st) q 24 h	Promotes ductal closure by inhibition of PGE_2 in the walls of the ductus	12–24 hours	Monitor renal function, bilirubin, electrolytes, glucose, platelets, bleeding
	0.1 mg/kg IV (2nd and 3rd)			
	>48 hours and <14 days: 0.3 mg/kg IV and 3 doses q 24 h			
	>14 days and <6 weeks: 0.2–0.3 mg/kg q 12 h			

BP, blood pressure; IV, intravenously; PDA, patent ductus arteriosus; PO, by mouth; q, every.

TABLE 7.10

DIGOXIN PRESCRIPTION INFORMATION

	TDD (mg/kg)	Maintenance Dose (mg/kg/day)
Preterm	0.025–0.05	0.008–0.012
Term	0.04–0.08	0.01–0.02 (1/8 TDD)

To digitalize:
1. Give 1/2 TDD
2. 6–8 hours later, give 1/4 TDD
3. 6–8 hours later, get a rhythm strip; if normal, give 1/4 TDD.
4. Give maintenance dose (1/8 TDD) 12 hours after last digitalizing dose and then every 12 hours.

Slow digitalization, with decreased risk of toxicity, can be achieved by starting with the maintenance dose.

TDD, total digitalizing dose.

diuretics interfere with the formation of free water and free water reabsorption by preventing the transport of sodium, potassium, and chloride into the medullary interstitium. Loop diuretics cause increased excretion of potassium by delivering increased quantities of sodium to sites in the distal nephron where potassium can be excreted. Furosemide also increases excretion of calcium but does not affect the ability of the kidney to regulate acid–base balance.

An aldosterone antagonist such as spironolactone (Aldactone) may be used because it is a potassium-sparing diuretic. Spironolactone works by binding to the cytoplasmic receptor sites and blocking aldosterone action, thus impairing the reabsorption of sodium and the secretion of potassium and hydrogen ion. Spironolactone has no effect on free water production and absorption. Thiazide diuretics (chlorothiazide and hydrochlorothiazide) inhibit sodium and chloride reabsorption along the distal tubules. They are not as effective as the loop diuretics and are infrequently used (Park, 2014).

Complications of Diuretic Therapy. Diuretic therapy can cause severe electrolyte imbalances if they are not monitored carefully. The complications of diuretic therapy include (1) volume contraction, (2) hyponatremia, (3) metabolic alkalemia or acidemia, and (4) hypokalemia or hyperkalemia. When using diuretics, fluid and electrolyte balance must be maintained by the administration of water and electrolytes. The adequacy of the volume can be determined by monitoring serum electrolytes, BUN, Cr, urinary output, weight, specific gravity, and skin turgor.

The increased renal losses of sodium can lead to hyponatremia, unless adequate amounts of sodium are provided. There may also be increased antidiuretic hormone (ADH) release secondary to changes in the osmoreceptors or inhibition of ADH action. Decreasing the amount of total water and improving the CO, thus increasing renal perfusion, can best manage this.

Metabolic alkalosis can result from administration of loop diuretics that interfere with sodium- and potassium-dependent chloride reabsorption. Hypochloremia results in a greater aldosterone production and an increase in bicarbonate concentration. Hypokalemia is a frequent complication of loop diuretic therapy. An increased ratio of intracellular to extracellular potassium results in the clinical signs and symptoms of hypokalemia. **Emergency Alert:** **Hypokalemia increases the risk for digoxin toxicity.** In contrast, hyperkalemia may result when CO is low and tissue perfusion is severely compromised. Other complications of diuretic therapy include increased calcium excretion, hyperuricemia, and glucose intolerance.

Subacute Bacterial Infective Endocarditis

Subacute bacterial infective endocarditis (SBIE or SBE) can be a complication in certain high-risk CHD patients. Two factors are important in the development of SBIE: (1) certain structural abnormalities that create turbulent flow or pressure gradients resulting in endothelial damage and (2) bacteremia. Certain CHDs and acquired heart disease with turbulent flow or a significant pressure gradient result in trauma to the endothelial lining, predisposing the endothelium to deposition of platelets and fibrin resulting in nonbacterial thrombotic endocarditis. If certain microbial species with pathogenic potential enter the bloodstream, there is potential to cause infective endocarditis at that site. Previously, more than 90% of infective endocarditis was due to *Streptococcus viridians, Streptococcus faecalis* (enterococcus), and *Staphylococcus aureus* but these organisms now only account for 50% to 60% of the cases, while fungi and HACEK (*Haemophilus influenzae, Aggregatibacter, Cardiobacterium, Eikenella,* and *Kingella spp)* organisms have increased. HACEK organisms account for 17% to 30% of the cases in neonates and immunocompromised children (Park, 2014).

Prevention. Based on the 2007 AHA guidelines, prevention of bacterial SBIE requires scrupulous daily oral care along with minimizing dental disease to decrease frequency of bacteremia in routine daily activities. SBIE prophylaxis is recommended for CHD patients considered at high risk for an adverse outcome (Box 7.4) with the following procedures: (1) all dental procedures; (2) respiratory tract procedures not including bronchoscopy; (3) procedures involving infected skin, skin structures, or musculoskeletal tissue. **Quality and Safety:** **Based on the 2007 AHA guidelines, antibiotic prophylaxis to prevent infective endocarditis is no longer recommended for gastrointestinal or genitourinary procedures.**

For further details and complete prescribing and dosing information, refer to the AHA Guidelines from the AHA Rheumatic Fever Endocarditis and Kawasaki Disease Committee of the Council on Cardiovascular Diseases in the Young (Wilson et al., 2007).

Neurodevelopmental Disabilities in CHD

Over 50% of CHD patients are at risk for ND problems, including mild learning disabilities, attention deficit disorder, and speech and motor problems. Children with HLHS and *d*-TGA have been the most widely studied cohort, and at least 50% of these patients are affected by ND issues that significantly impact their academic achievement and quality of life. Several studies have demonstrated that 17% to 40% of neonates with complex congenital heart disease have evidence of periventricular leukomalacia (PVL) on preoperative MRI, whereas 50% had evidence of PVL on postoperative MRI. White matter injury or PVL has been associated with ND problems and impaired functional outcomes in very low birthweight and preterm neonates. By the time CHD patients reach school age, there are notable deficiencies in fine and gross motor functions, tests of intelligence and achievement, speech, language, and behavior (Bellinger et al., 2003; Galli et al., 2004; Goff et al., 2014; Hovels-Gurich et al., 2007; Mahle et al., 2002; Marelli, Miller, Marino, Jefferson, & Newburger, 2016; Marino et al., 2012).

Box 7.4

CARDIAC CONDITIONS FOR WHICH SBIE PROPHYLAXIS IS RECOMMENDED

1. Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
2. Previous history of infective endocarditis
3. CHD
   - Unrepaired cyanotic CHD including palliative shunts and conduits
   - Unrepaired CHD with prosthetic material or device whether placed by surgery or cardiac catheterization during the first 6 months after the procedure
   - Repaired CHD with a residual defect at the site or adjacent to a prosthetic patch or device (that inhibits endothelialization)
4. Cardiac transplant recipient who developed cardiac valvulopathy

CHD, congenital heart disease.

Source: Adapted from Wilson, W., Taubert, K. A., Gewitz, M., Lockhart, P. B., Baddour, L. M., Levison, M., . . . Durack, D. T. (2007). Prevention of infective endocarditis: Guidelines from the American Heart Association: A guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation, 116*(15), 1736–1754. doi:10.1161/CIRCULATIONAHA.106.183095

Family Support

Families of infants who are critically ill or have congenital defects generally experience confusion, guilt, anger, and fear. The family must cope with short- and long-term consequences of the CHD. Severity of the defect, availability of treatment, and prognosis influence the amount and type of support required. Parents may be overwhelmed by the knowledge of their infant's heart defect, regardless of the severity. With treatment now available, over 95% of CHDs can be palliated or fully corrected through a combination of medical and surgical management (Cooley, 1997). However, residual defects or cardiovascular sequelae after surgical correction are common (Meberg, Otterstad, Frøland, Lindberg, & Sørland, 2000). Parents need to be able to discuss quality-of-life issues with healthcare professionals in order to make informed decisions about possible treatment options (Møyen et al., 1997). All options must be explained and described objectively. The impact of the cardiac defect on other systems must also be included when giving parents information, as the parents may not be aware of the associated complications, such as respiratory problems, that often accompany cardiac defects (Lubica, 1996). Although often overlooked, neurologic prognosis is a key factor in determining the overall quality of life of a child with a CHD. Pediatric neurologists can be integrated into the healthcare team to assist parents in assessing the neurologic prognosis of their child as well as beginning early intervention programs to facilitate the best outcomes (Shevell, 1999). Parents need frequent contact with members of the healthcare team. Caretakers should speak with parents routinely, not just when there are major changes in the infant's condition.

Although most CHDs do not have an identifiable genetic pattern, genetic counseling should be offered to all parents with a newborn with a CHD. Parents will want answers to questions about the cause of the defect, the likelihood of a recurrence in future pregnancies, and if there may be associated defects (Welch & Brown, 2000; Wolf & Basson, 2010). In addition, improving ultrasound screening for CHD may improve prenatal detection of CHD (Bakiler, Ozer, Kanik, Kanit, & Aktas, 2007; Landis et al., 2013), thus increasing the opportunity for fetal surgery for correction of some defects, improved immediate management at birth, or, in some cases, termination of the pregnancy. Most CHDs can be identified with 18-to-20–week anatomy scans, with almost 90% of CHD prenatally detected if the four-chamber and outflow tract views are visualized (Sklansky, Berman, Pruetz, & Chang, 2009) Despite updated guidelines, in some regions of the United States, the lower prenatal detection rate may be a result of inadequate prenatal screening (Goff, personal communication). Healthcare professionals must be keenly aware of all options to assure that parents receive the most up-to-date information on which to base decisions.

One of the defect diagrams and models illustrating the defect should be used. Parents need frequent reassurance and repetition of information. Parents of infants who do not require immediate surgery but who will eventually require surgical correction must be educated about all aspects of the infant's care, including signs and symptoms of deterioration, medication administration, activity limitations, and normal development. Because growth failure with a cardiac defect is common, efforts to maximize nutrition are important; extra support is needed if the mother plans to breastfeed her baby (Barbas & Kelleher, 2004; Varan, Tokel, & Yilmaz, 1999). Careful follow-up is important to prevent complications.

Identification of support persons for the family is extremely valuable. Parents may be encouraged to talk to other parents of newborns with the same or similar defects. Many neonatal intensive care units (NICUs) have active support groups consisting of parents of patients. Care should be taken in selection of supporters. Parents with a term newborn with a CHD may not be able to relate to parents of a preterm neonate. Other family members or friends should not be overlooked; they can become valuable support persons if they are provided appropriate guidance and education. The needs of siblings should also be assessed. Siblings need support, education, and guidance appropriate for their age and comprehension of the situation. Parents may not recognize their needs because of the overwhelming situation. Healthcare providers can facilitate the parent–child relationship during the initial period and throughout the course of the management.

Financial resources should be addressed because preoperative, operative, and postoperative care is expensive. Many parents need assistance in obtaining aid to which they are entitled. Even the most knowledgeable of parents may not be aware of resources available to them. If experimental surgery is contemplated, parents may need assistance speaking to private insurance companies regarding coverage. Referrals to appropriate local, state, federal, or private organizations that pertain to the CHD should be made for the parents. These include the Department of Family and Children Services, the March of Dimes, and Children's Medical Services. The family may qualify for the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC).

Discharge planning must be comprehensive for the neonate who will receive medical management for a CHD before corrective surgery. A thorough assessment of the home may be needed before discharge. Contact with the primary care provider who will

perform the routine management of the infant is imperative. Initial contact by telephone should be followed up with a copy of the complete medical record and discharge summary. If the infant requires any special equipment for home care, the equipment should be obtained before discharge so that the parents can be taught how to use it. Also, practical details such as whether there are enough electrical outlets in the infant's room must be determined. Notification of local emergency medical services, power companies, and other relevant companies should be completed before discharge.

SUMMARY

The most common CHD lesions are reviewed along with the most common arrhythmias seen in the newborn. The diagnosis and management of the most frequent complications of CHDs, CHF, and recommendations of SBIE are included. Parental support of families with newborns and children with CHDs has been discussed.

CASE STUDY

The NICU in a large women and children's hospital received a call for assistance from the adjacent Mother and Baby Unit to evaluate an infant for cyanosis. Nurse Johnson responded to the call and discovered that Baby Johanna was pale, cyanotic, and tachypneic. She positioned the baby for optimal oxygenation and supplied oxygen via blow-by. Baby Johanna responded to the blow-by oxygen with improved color and tone. Nurse Johnson told the mother that she would take the baby to the NICU for further evaluation and update her as soon as possible. In the NICU, the baby's pediatrician was called and the birth history was obtained from the medical record supplied by the Mother and Baby Unit personnel. Baby Johanna was put in an oxyhood, and vital signs were obtained. The baby was now pink, HR was 164, respiratory rate was 76, and the mean blood pressure was 58.

Johanna was born to a gravida 1, para 0 (now 1), 24-year-old mother with uncomplicated pregnancy and delivery. Birthweight was 3.3 kg, and Apgar scores were 8/9 (−1 color, −1 tone, −1 color). Johanna showed no distress, and the pediatrician's examination at 3 hours post birth was within normal limits, with some slight acrocyanosis of the hands and feet present. Johanna had been in the Mother and Baby Unit and the mother was nursing. At this feeding, the mother had offered the baby a bottle following nursing. She called the floor nurse because the baby seemed to turn blue during the feeding.

Upon auscultation, a soft ejection-type murmur was noted at the upper left sternal border. Right radial arterial blood gas showed a partially compensated metabolic acidosis on 70% Fio_2 per hood. The pulse oximeter registered an oxygen saturation of 58% on arms and legs. A hyperoxia test using 100% Fio_2 showed no improvement in arterial oxygenation. The cardiac murmur had increased and was determined to be systolic in origin, and probably tricuspid regurgitation. Chest x-ray showed normal heart size and decreased pulmonary markings. A stat echocardiogram was ordered to determine whether a cardiac defect was present.

1. What other intervention should be initiated while the definitive diagnosis is being obtained?
2. What are the most likely cardiac defects with this presentation?
3. How does the timing of the episode influence the differential diagnosis?
   Echocardiography revealed presence of PA/IVS with a PDA providing left-to-right flow into the pulmonary system. The PDA was maintained by the continuous infusion of PGE_1 started after the chest x-ray was obtained.
4. What is the general management for PA/IVS?
5. What information should be shared with the parents regarding short- and long-term treatment and prognosis?

EVIDENCE-BASED PRACTICE BOX

Screening for Critical Congenital Heart Defects With Pulse Oximetry

The overall incidence of CHD is slightly less than 1%, or 8 per 1,000 live births, excluding PDA in the preterm newborn, which is the single largest factor for infant mortality due to all birth defects. CHDs that usually cause hypoxia in the newborn period and are associated with the highest mortality are classified as *critical congenital heart defects* (CCHDs). Newborns with CCHDs require immediate intervention to prevent death or disability.

Seven cardiac defects make up the CCHDs: HLHS, PA/IVS, TOF, TAPVR, TGA, tricuspid atresia, and truncus arteriosus. Approximately 4,800 babies are born each year in the United States with one of these seven CCHDs.

Delayed diagnosis of any of these defects significantly increases the risk for morbidity or mortality. Currently, diagnosis depends on prenatal ultrasound identification or physical examination of the newborn. This approach does not identify all defects, and so it leads to late diagnosis and increased morbidity and sometimes mortality. Methods that allow earlier identification of these cardiac defects would lead to quicker diagnosis, implementation of treatment, and improved outcome.

Routine screening of newborns with pulse oximetry was proposed as one method to improve early diagnosis of CCHDs. Pulse oximetry is a noninvasive, painless, relatively inexpensive, and readily available method that measures blood oxygen saturation. Most CCHDs are associated with hypoxia, and thus pulse oximetry screening could identify newborns with one of these defects. Numerous studies were conducted in the United States and in other countries, including Sweden and Germany, to determine whether routine pulse oximetry measurements on newborns improved the detection of CCHDs.

The U.S. Health and Human Services Secretary convened a group of experts to examine evidence of the effectiveness of pulse oximetry screening. The group consisted of members recommended by the Secretary's Advisory Committee on Heritable Diseases in Newborns and Children, the American Academy of Pediatrics (AAP), the American College of Cardiology

(*continued*)

EVIDENCE-BASED PRACTICE BOX (*continued*)

Foundation, and the American Heart Association. The work group found sufficient evidence to recommend routine screening with pulse oximetry monitoring to identify low blood oxygen saturation in newborns in well-infant and intermediate nurseries. They recommended further study for screening of special populations, such as those who live in high altitudes.

Based on this review of the evidence, Secretary of Health and Human Services Kathleen Sebelius recommended the addition of pulse oximetry screening for CCHD in newborns in 2011. This recommendation was officially endorsed by the AAP. Most hospitals have adopted this screening method; however, there are differences in the screening process, in the number and type of conditions that are screened for in each state, and in the data collection to review efficacy of the program. As of 2015, most states have introduced or passed legislation to add pulse oximetry screening to the current newborn screening, but not all states have mandated pulse oximetry screening and data reporting. See the status of legislation in your state at this website: www.cdc.gov/ncbddd/heartdefects/documents/2015-critical-chd-newborn-screening-by-state.pdf

Many hospitals have implemented the screening process and have organized reporting voluntarily. This is an example of evidence-based practice change.

PARENT VOICES

Farrin Moreno

My micropreemie was born at 25 weeks' gestational age. The doctors assured me she had 0% chance of survival. In fact, while hospitalized for 6 weeks on strict bed rest leading up to her birth, my doctor tirelessly tried convincing me to terminate my pregnancy. My daughter weighed 1 lb 7 ounces and was 12 inches long. She was placed on a ventilator immediately following her birth, but on her second day of life she began breathing over it. She graduated to a nasal cannula. At 1 week of age, her breathing became harder to regulate and her weight began to drop. After several tests, we were told she had a congenital heart defect called patent ductus arteriosus (PDA). The medical team said the PDA required a surgical closure to prevent blood from getting into her lungs. Their attempt to comfort me failed miserably as they said, "It's just a PDA, these are so common in preemies," driving me to think I was irrational for being terrified. I felt alone. The PDA ligation was performed when she was 2 weeks old. Still on a ventilator following the surgery, her progress remained slow. She developed three staph infections and remained on the ventilator nearly 2 weeks post surgery. Almost a month later, I held my baby girl for 2 short minutes before the alarms attached to her tiny body began to sound. Nurses should know that every step a parent takes toward the NICU doors, they can already hear the gut-wrenching alarms echoing throughout the unit, often mentally preparing them for the worst possible news. I wish my daughter's nurses knew that though I was an unwed, 19-year-old, first-time mom, I fought every day for my child to have a chance at life, even if it meant risking mine. If only the nurses knew how much it hurt when I mustered up the courage to ask if I could change a diaper, take a temperature, or do anything that mommies do, but was told, "No, thank you" as if I were a guest. If only the nurses let me try kangaroo care. I desperately wanted to bond with her but felt completely helpless, as pumping breastmilk seemed like my only contribution. I wish they had known that every NICU interaction would be permanently engrained in my mind. Once a nurse handed me my daughter's laundry bag asking if I thought I could "handle" washing her clothing with hypoallergenic detergent. I remember feeling 2 feet tall. Another time, I rushed to the hospital to get my freshly pumped breastmilk to my daughter before her next feeding, but arrived just as her nurse began feeding her formula while looking at me saying I would need to "do better" if I expected my daughter to have an exclusive breastmilk diet. I wish her nurses knew how much their verbal and nonverbal communication impacted my life well beyond the NICU, and how the trauma earned in the NICU does not go away. How you communicate matters.

ONLINE RESOURCES

American Academy of Pediatrics. (2009). *Role of pulse oximetry in examining newborns for congenital heart disease: A scientific statement from the AHA and AAP*. Retrieved from http://pediatrics.aappublications.org/content/124/2/823.short

Centers for Disease Control and Prevention. (n.d.). Screening for critical congenital heart defects. Retrieved from https://www.cdc.gov/ncbddd/heartdefects/screening.html

Interagency Coordinating Committee on Screening in Newborns and Children. (n.d.). *Screening for critical congenital heart disease: A Federal Agency Plan of Action*. Retrieved from http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/recommendations/correspondence/cyanoticheartsecre09212011.pdf

Thangaratinam, S., Brown, K., Zamora, J., Khan, K. S., & Ewer, A. K. (2012). Pulse oximetry screening for CCHDs in asymptomatic newborn babies: A systematic review and meta-analysis. *Lancet, 379*(9835), 2459–2464. doi:10.1016/S0140-6736(12)60107-X

REFERENCES

Anuwutnavin, S., Satou, G., Chang, R. K., DeVore, G. R., Abuel, A., & Sklansky, M. (2016). Prenatal sonographic predictors of neonatal coarctation of aorta. *Journal of Ultrasound in Medicine, 35*(11), 2353–2364. doi:10.7863/ultra.15.06049

Bakiler, A. R., Ozer, E. A., Kanik, A., Kanit, H., & Aktas, F. N. (2007). Accuracy of prenatal diagnosis of congenital heart disease with fetal echocardiography. *Fetal Diagnostic Therapy, 22*(4), 241–244. doi:10.1159/000100782

Barbas, K. H., & Kelleher, D. K. (2004). Breastfeeding success among infants with congenital heart disease. *Pediatric Nursing, 30*(4), 285–289. https://www.researchgate.net/profile/Kimberly_Barbas/publication/8206302_Breastfeeding_success_among_infants_with_congenital_heart_disease/links/54e398cb0cf2b2314f5db2b0/Breastfeeding-success-among-infants-with-congenital-heart-disease.pdf

Brown, D. C., & Geva, T. (2016). Anomalies of the pulmonary veins. In H. D. Allen, R. E. Shaddy, D. J. Penny, T. F. Feltes, & F. Cetta (Eds.), *Moss and Adams heart disease in infants, children and adolescents*. (9th ed., Vol. 2, pp. 881–910). Philadelphia, PA: Lippincott Williams & Wilkins.

Cooley, D. A. (1997). Early development of congenital heart surgery: Open heart procedures. *The Annals of Thoracic Surgery, 64*(5), 1544–1548. doi:10.1016/S0003-4975(97)01025-4

Danford, D. A., Gumbiner, C. H., Martin, A. B., & Fletcher, S. E. (2000). Effects of electrocardiography and chest radiography on the accuracy of preliminary diagnosis of common congenital cardiac defects. *Pediatric Cardiology, 21*(4), 334–340. doi:10.1007/s002460010075

Danford, D. A., Salaymeb, K. J., Martin, A. B., Fletcher, S. E., & Gumbiner, C. H. (1999). Pulmonary stenosis: Defect-specific diagnostic accuracy of heart murmurs in children. *Journal of Pediatrics, 134*(1), 76–81. doi:10.1016/S0022-3476(99)70375-6

Dipchand, A. I., Giuffre, M., & Freedom, R. M. (1999). Tetralogy of Fallot with non-confluent pulmonary arteries and aortopulmonary septal defect. *Cardiology in the Young, 9*(1), 75–77. doi:10.1017/S1047951100007459

Donofrio, M., Moon-Grady, L., Hornberger, L., Copel, J., Sklansky, M. S., Abuhamad, A., . . . Rychik, J.; (2014). Diagnosis and treatment of fetal cardiac disease. A scientific statement from American Heart Association. *Circulation, 129*(21), 2183–2242. doi:10.1161/01.cir.0000437597.44550.5d

Eckersley, L., Sadler, L., Parry, E., Finucane, K., & Gentles, T. L. (2016, June). Timing of diagnosis affects mortality in critical congenital heart disease. *Archives of Disease in Childhood, 101*(6), 516–520. doi:10.1136/archdischild-2014-307691

Freedom, R. M., Yoo, S. -J., & Coles, J. G. (2007). Atrioventricular septal defect. In R. M. Freedom, S.-J. Yoo, H. Mikailian, & W. G. Williams (Eds.), *The natural and modified history of congenital heart disease* (pp. 44–55). Elmsford, NY: Blackwell Publishing. doi:10.1002/9780470986905.ch5

Galli, K. K., Zimmerman, R. A., Jarvik, G. P., Wernovsky, G., Kuypers, M. K., Clancy, R. R., . . . Gaynor, J. W. (2004). Periventricular leukomalacia is common after neonatal cardiac surgery. *The Journal of Thoracic and Cardiovascular Surgery, 127*(3), 692–704. doi:10.1016/j.jtcvs.2003.09.053

Gilboa, S. M., Salemi, J. L., Nembhard, W. N., Fixler, D. E., & Correa, A. (2010). Mortality resulting from congenital heart disease among children and adults in the United States, 1999-2006. *Circulation, 122*(22), 2254–2263. doi:10.1161/CIRCULATIONAHA.110.947002

Godfrey, M., & Rychik, J. (2012). The fetal circulation. In J. Rychik & Z. Tian (Eds.), *Fetal cardiovascular imaging* (1st ed., pp. 2–7). Philadelphia, PA: Elsevier.

Goff, D. A., Blume E. D., Gauvreau, K., Mayer J. E., Lock J. E., & Jenkins K. J. (2000). Clinical outcome of fenestrated Fontan patients after closure—the first 10 years. *Circulation, 102*, 2094–2099. doi:10.1161/01.CIR.102.17.2094

Goff, D. A., Shera, D., Tang, S., Lavin, N. A., Durning, S., Nicolson, S. C., . . . Licht, D. J. (2014). Risk factors for preoperative periventricular leukomalacia in term neonates with hypoplastic left heart syndrome are patient related. *The Journal of Thoracic and Cardiovascular Surgery, 147*(4), 1312–1318. doi:10.1016/j.jtcvs.2013.06.021

Goldmuntz, E., & Crenshaw, M. L. (2016). Genetic aspects of congenital heart defects. In H. D. Allen, R. E. Shaddy, D. J. Penny, T. F. Feltes, & F. Cetta (Eds.), *Moss and Adams heart disease in infants, children and adolescents* (9th ed., Vol. 1, pp. 87–116). Philadelphia, PA: Lippincott Williams & Wilkins.

Hanley, F. L., Sade, R. M., Blackstone, E. H., Kirklin, J. W., Freedom R. M., & Nanda, N. C. (1993). Outcomes in neonatal pulmonary atresia with intact ventricular septum. A multiinstitutional study. *The Journal of Thoracic and Cardiovascular Surgery, 105*(3), 406–423.

Hornberger, L. (2006). Maternal diabetes and the fetal heart. *Heart, 92*(8), 1019–1021. doi:10.1136/hrt.2005.083840

Hovels-Gurich, H. H., Konrad, K., Skorzenski, D., Herpertz-Dahlmann, B., Messmer, B. J., & Seghaye, M. C. (2007). Attentional dysfunction in children after corrective cardiac surgery in infancy. *The Annals of Thoracic Surgery, 83*(4), 1425–1430. doi:10.1016/j.athoracsur.2006.10.069

Jacobs, J. P., Mayer, J. E., Jr., Pasquali, S. K., Hill, K. D., Overman, D. M., St. Louis, J.D., . . . Jacobs, M. L. (2018, March). The Society of Thoracic Surgeons Congenital Heart Surgery Database: 2018 update on outcomes and quality. *The Annals of Thoracic Surgery, 105*(3), 680–689. doi:10.1016/j.athoracsur.2018.01.001

Jones, K. (2005). *Smith's recognizable patterns of human malformation* (6th ed.). Philadelphia, PA: Saunders.

Kaplan, N. M. (2011). Systemic hypertension therapy. In R. Bonow, D. Mann, D. P. Zipes, P. Libby, & E. Braunwald (Eds.), *Braunwald's heart disease: A textbook of cardiovascular medicine* (pp. 955–975). Philadelphia, PA: WB Saunders.

Koch, J., Hensley, G., Roy, L., Brown, S., Ramaciotti, C., & Rosenfeld, C. (2006). Prevalence of spontaneous closure of the ductus arteriosus in neonates at a birth weight of 1000 grams or less. *Pediatrics, 117*(4), 1113–1121. doi:10.1542/peds.2005-1528

Kushnir, A., & Pinheiro, J. M. (2011). Comparison of renal effects of ibuprofen versus indomethacin during treatment of patent ductus arteriosus in contiguous historical cohorts. *BMC Clinical Pharmacology, 11*, 8. doi:10.1186/1472-6904-11-8

Landis, B. J., Levey, A., Levasseur, S. M., Glickstein, J. S., Kleinman, C. S., Simpson, L. L., & Williams, I. A. (2013). Prenatal diagnosis of congenital heart disease and birth outcomes. *Pediatric Cardiology, 34*(3), 597–605. doi:10.1007/s00246-012-0504-4

Lubica, H. (1996). Pathologic lung function in children and adolescents with congenital heart defects. *Pediatric Cardiology, 17*(5), 314–315. doi:10.1007/s002469900068

Mahle, W. T., Tavani, F., Zimmerman, R. A., Nicolson, S. C., Galli, K. K., Gaynor, J. W., . . ., Kurth, C. D. (2002), An MRI study of neurological injury before and after congenital heart surgery. *Circulation, 106*(12 Suppl. 1), I109– I114. Retrieved from https://www.ahajournals.org/doi/full/10.1161/01.cir.0000032908.33237.b1

Mann, D. (2012). Pathophysiology of heart failure. In R. O. Bonow, D. Mann, D. P. Zipes, P. Libby, & E. Braunwald (Eds.), *Braunwald's heart disease: A textbook of cardiovascular medicine* (pp. 487–504). Philadelphia, PA: WB Saunders.

Marelli, A., Miller, S.P., Marino, B.S., Jefferson, A.L., & Newburger, J.W. (2016). Brain in congenital heart disease across the lifespan: The cumulative burden of injury. *Circulation, 133*(20), 1951–1962. doi:10.1161/CIRCULATIONAHA.115.019881

Marino, B. S., Lipkin, P. H., Newburger, J. W., Peacock, G., Gerdes, M., Gaynor, J. W., . . ., Mahle, W. T. (2012). Neurodevelopmental outcomes in congenital heart disease: Evaluation and management. *Circulation, 126*(9), 1143–1172. doi:10.1161/CIR.0b013e318265ee8a

Marino, B. S., Ostrow, A. M., & Cohen, M. S. (2006). Surgery for congenital heart disease. In V. Vetter (Ed.), *Pediatric cardiology: The requisites in pediatrics* (pp. 277–320). Philadelphia, PA: Mosby Elsevier.

Massimo, S. S., Drago, F., Grutter, G., De Santis, A., Di Ciommo, V., & Rava, L. (2006). Twenty years of paediatric cardiac pacing: 515 pacemakers and 480 leads implanted in 292 patients. *Europace, 8*(7), 530–536. doi:10.1093/europace/eul062

Massin, M. M., Derkenne, B., & von Bernuth, G. (1998). Heart rate behavior in children with atrial septal defect. *Cardiology, 90*(4), 269–270. doi:10.1159/000006857

McElhinney, D. B., Paridon, S., & Spray, T. L. (2000). Aortopulmonary window associated with complete atrioventricular septal defect. *The Journal of Thoracic and Cardiovascular Surgery, 119*(6), 1284–1285. doi:10.1067/mtc.2000.106033

Meberg, A., Otterstad, J. E., Frøland, G., Lindberg, H., & Sørland, S. J. (2000). Outcome of congenital heart defects—A population-based study. *Acta Paediatrica, 89*(11), 1344–1351. doi:10.1111/j.1651-2227.2000.tb00763.x

Møyen Laane, K., Meberg, A., Otterstad, J. E., Frøland, G., Sørland, S., Lindstrom, B., & Erickson, B. (1997). Quality of life in children with congenital heart defects. *Acta Paediatrica, 86*(9), 975–980. doi:10.1111/j.1651-2227.1997.tb15182.x

Nouri, S. (1997). Congenital heart defects: Cyanotic and acyanotic. *Pediatric Annals, 26*(2), 95–98. doi:10.3928/0090-4481-19970201-06

O'Connor, M. J., & Shah, M. J. (2012). Arrhythmias in the fetus. In J. Rychik & Z. Tian (Eds.), *Fetal cardiovascular imaging*. (1st ed., pp. 477–491). Philadelphia, PA: Elsevier.

Olgin, J. E., & Zipes, D. P. (2012). Specific arrhythmias: Diagnosis and treatment. In R. Bonow, D. Mann, D. P. Zipes, P. Libby, & E. Braunwald (Eds.), *Braunwald's heart disease: A textbook of cardiovascular medicine* (9th ed., pp. 771–824). St. Louis, MO: WB Saunders.

Opie, L. H., & Hasenfuss, G. (2012). Mechanisms of cardiac contraction and relaxation. In R. Bonow, D. Mann, D. P. Zipes, P. Libby, & E. Braunwald (Eds.), *Braunwald's heart disease: A textbook of cardiovascular medicine* (pp. 459–486). Philadelphia, PA: WB Saunders.

Park, M. K. (2014). *Pediatric cardiology for practitioners*. Chicago, IL: Mosby.

Quartermain, M. D., Pasquali S. K., Hill, K. D., Goldberg, D. J., Huhta, J. C., Jacobs J. P., . . ., Ungerleider, R. M. (2015). Variation in prenatal diagnosis of congenital heart disease in infants. *Pediatrics, 136*(2), e378–e385. doi:10.1542/peds.2014-3783

Rudolph, A. M. (2001). *Congenital diseases of the heart. Clinical-physiological considerations*. Armonk, NY: Futura Publishing

Russo, P., & Russo, J. G. (2005). Congenital heart defects in newborns and infants: Cardiothoracic repair. In A. R. Spitzer (Ed.), *Intensive care of the fetus & neonate* (2nd ed., pp. 939–953). Philadelphia, PA: Elsevier.

Rychik, J. (2012). Fetal cardiomyopathy. In J. Rychik & Z. Tian (Eds.), *Fetal cardiovascular imaging* (1st ed., pp. 376–381). Philadelphia, PA: Elsevier.

Sacchetti, A., Moyer, V., Baricella, R., Cameron, J., & Moakes, M. E. (1999). Primary cardiac arrhythmias in children. *Pediatric Emergency Care, 15*(2), 95–98. doi:10.1097/00006565-199904000-00004

Schultz, A. H., & Kreutzer, J. (2006). Cyanotic heart disease. In V. Vetter (Ed.), *Pediatric cardiology: The requisites in pediatrics* (pp. 51–78). Philadelphia, PA: Mosby Elsevier.

Seidman, J. G., Pyeritz, R., & Seidman, C. (2012). Inherited causes of cardiovascular disease. In R. Bonow, D. Mann, D. P. Zipes, P. Libby, & E. Braunwald (Eds.), *Braunwald's heart disease: A textbook of cardiovascular medicine* (9th ed., pp. 70–80). Philadelphia, PA: WB Saunders.

Sekar, K. C., & Corff, K. E. (2008). Treatment of patent ductus arteriosus: Indomethacin or ibuprofen? *Journal of Perinatology, 28*(Suppl. 1), S60–S62. doi:10.1038/jp.2008.52

Shevell, M. I. (1999). The role of the pediatric neurologist in the management of children with congenital heart defects: A commentary. *Seminars in Pediatric Neurology, 6*(1), 64–66. doi:10.1016/S1071-9091(99)80048-5

Sklansky, M. S., Berman, D. P., Pruetz, J. D., & Chang R. R. (2009). Prenatal screening for congenital heart disease: Superiority of outflow tracts over four chamber view. *Journal of Ultrasound in Medicine, 28*(7), 889–899. doi:10.7863/jum.2009.28.7.889

Taussig, W. B. (1947). *Cyanosis in congenital malformations of the heart*. New York, NY: Oxford University Press.

Turner, S. W., Hunter, S., & Wyllie, J. P. (1999). The natural history of ventricular septal defects. *Archives of Disease in Childhood, 81*(5), 413–416. doi:10.1136/adc.81.5.413

Varan, B., Tokel, K., & Yilmaz, G. (1999). Malnutrition and growth failure in cyanotic and acyanotic congenital heart disease with and without pulmonary hypertension. *Archives of Disease in Children, 81*(1), 49–52. doi:10.1136/adc.81.1.49

Verklan, M. T., & Walden, M. (2004). *Core curriculum for neonatal intensive care nursing*. St. Louis, MO: Elsevier Saunders.

Webb, G., Smallhorn, J., Therrien, J., & Redington, A. (2012). Congenital heart disease. In R. Bonow, D. Mann, D. P. Zipes, P. Libby, & E. Braunwald (Eds.), *Braunwald's heart disease: A textbook of cardiovascular medicine* (9th ed., pp. 1411–1467). Philadelphia, PA: WB Saunders.

Welch, K. K., & Brown, S. A. (2000). The role of genetic counseling in the management of prenatally detected congenital heart defects. *Seminars in Perinatology, 24*(5), 373–379. doi:10.1053/sper.2000.16547

Wernovsky, G., & Gruber, P. J. (2005). Common congenital heart disease: Presentation, management, and outcomes. In H. W. Taeusch, R. A. Ballard, & C. A. Gleason (Eds.), *Avery's diseases of the newborn* (8th ed., pp. 827–871). Philadelphia, PA: Elsevier.

Wilson, W., Taubert, K. A., Gewitz, M., Lockhart, P. B., Baddour, L. M., Levison, M., . . . Durack, D. T. (2007). Prevention of infective endocarditis: Guidelines from the American Heart Association: A guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation, 116*(15), 1736–1754. doi:10.1161/CIRCULATIONAHA.106.183095

Wolf, M., & Basson, C. (2010). The molecular genetics of congenital heart disease: A review of recent developments. *Current Opinion Cardiology, 25*(3), 192–197. doi:10.1097/HCO.0b013e328337b4ce

CHAPTER 8

Gastrointestinal System

Khiet D. Ngo and Manoj Shah

INTRODUCTION

The intake and digestion of food and the elimination of waste products are critical to long-term survival. Although many complex metabolic processes are involved, the ability to maintain adequate nutrition ultimately requires that the gastrointestinal (GI) tract be patent and structurally intact. With only a few exceptions, the vast majority of conditions causing GI dysfunction are the result of congenital anatomic malformations. The discovery and management of GI dysfunction requires knowledge of both embryogenesis and normal anatomy and physiology. External defects are immediately apparent, but most causes of dysfunction have few initial symptoms unless allowed to progress to serious pathophysiologic changes resulting in a major threat to life. The input and support of a variety of nursing, medical, and other specialists are required for optimizing outcomes of the infant's physiologic well-being and the parents' psychosocial stability. Visible defects, especially those involving the face, appear to be particularly difficult for parents to accept. GI malformations, often associated with other congenital anomalies and prematurity, and the need for transport to a distant center where corrective surgery can be accomplished place additional demands on parental coping.

Parents' emotional needs and their ability to work through the grief process over the loss of the expected "perfect" child cannot be underestimated.

The GI tract is the site of the many complex transport and enzymatic mechanisms required for the absorption and digestion of nutrients. The successful intake and assimilation of these nutrients, however, rest on the ability of the gut to act as a conduit for ingestion, digestion, and elimination. Congenital malformations, particularly those involving anatomic or functional obstruction, clearly hinder this process. Even when structurally intact, the supporting gastric and intestinal musculature of the newborn is relatively deficient, increasing the tendency toward abdominal distention as a result of infrequent and irregular peristaltic movements. Transport of materials through the tract is further diminished in premature infants, who may have poor sucking and swallowing abilities, small gastric capacity, and an incompetent gastroesophageal sphincter. Debilitated, hypotonic infants may similarly exhibit poor sucking and swallowing and decreased GI motility. In addition, the bowel seems particularly susceptible to ischemic conditions in which blood flow is preferentially directed away from the GI tract, the kidneys, and the peripheral vascular bed toward the brain and heart.

Untoward effects of drugs commonly used in the nursery may further compromise intestinal function or integrity. Morphine, for example, in addition to its desired analgesic effect, also slows gastric emptying and reduces propulsive peristalsis. Conversely, erythromycin has been shown to accelerate gastric emptying. Ulceration of the GI tract with possible bleeding and perforation are reported side effects of tolazoline, dexamethasone, and indomethacin (Zenk, Sills, & Koeppel, 2003). Mydriatics administered for ophthalmologic examination in the preterm infant decrease duodenal activity and gastric emptying (James, 2002). Xanthines may cause or exacerbate gastroesophageal reflux (GER; Jadcherla, 2002). The major purposes of this chapter are to discuss the embryologic development and normal anatomic structure and physiology of the GI tract and to describe common causes of neonatal dysfunction and their implications for care.

EMBRYOLOGY

Formation of the GI tract largely depends on the folding of the embryo during the first month of development. At the beginning of the third week of gestation, as a result of the neural plate development, the flat, trilaminar embryonic disk begins to fold in both a cephalic-caudal and a ventral direction, invaginating the dorsal portion of the yolk sac. By the fourth week, this folding is complete, resulting in a horseshoe-shaped cylinder. This hollow tube is divided into three sections corresponding to the foregut, the midgut, and the hindgut.

Foregut

The foregut forms part of the mouth, esophagus, stomach, proximal duodenum, pancreas, liver, and extrahepatic biliary system as well as the lower respiratory system. The most cranial area of the foregut is often known as the pharyngeal gut. Early in the fourth week of fetal life, a depression appears on the ventral surface of the head called the stomodeum or primitive mouth. Oval thickenings, the nasal placodes, develop above and on either side of the primitive mouth, eventually becoming the nostrils. These nasal elevations and the area above the stomodeum merge to form the philtrum. By the eighth week, a continuous ridge forming the upper lip has developed from maxillary processes on either side

of the stomodeum fusing with the nasal pits and philtrum. The lower lip and jaw are formed when two mandibular processes below the stomodeum grow and fuse. Beginning in the fifth week, the primary palate begins to form from a wedge-shaped extension of the maxillary processes, thus separating the future nostrils from the upper lip. Lateral palatine processes also form on each side of the tongue and fuse with the nasal septum, anteriorly progressing posteriorly to form the secondary palate during the 9th to 12th week of development.

At the same time that the mouth is formed, the rest of the foregut is also developing. During the fourth and fifth weeks of gestation, an esophagotracheal septum is formed dividing the proximal foregut into the anterior trachea and posterior esophagus. Initially short, the esophagus elongates over a 2- to 3-week period to allow the development of the lungs, heart, and neck.

The stomach, first appearing as a dilation of the foregut, begins to grow with the dorsal aspect outpacing the ventral aspect, thus forming the greater curvature. As the esophagus grows, the stomach initially in the region of the neck descends and rotates 90° on its longitudinal axis until it reaches its final position. The duodenum develops from the caudal portion of the foregut as well as the cranial portion of the midgut. Around the fifth or sixth week, villi grow and temporarily occlude the lumen until the 9th or 10th week of gestation. Several other buds on the foregut also form the liver, gallbladder, bile ducts, and pancreas.

Midgut

The midgut consists of the distal duodenum, jejunum, ileum, cecum, appendix, ascending colon, and the right two-thirds of the transverse colon. Blood is supplied by the superior mesenteric artery. Although initially in tandem, the lengthening of the tubular intestine outpaces the overall elongation of the embryo.

By the sixth week of gestation, the rate of growth causes the tube to bend ventrally. Simultaneously, rapid growth of the liver quickly limits space within the abdominal cavity. Consequently, around 7 weeks' gestation, loops of intestine begin to protrude into the umbilical cord. As the midgut herniates, it rotates in a counterclockwise fashion approximately 90° around an axis formed by the superior mesenteric artery. At around 10 weeks, when the abdominal cavity has expanded sufficiently and the growth of the liver has slowed, reduction of the midgut herniation occurs. As the loops of intestine are retracted into the abdomen, they rotate another 180°, resulting in a full rotation of 270°. This counterclockwise rotation allows the transverse colon to pass in front of the duodenum and places the cecum and appendix in the right lower quadrant of the abdomen. Once the intestine has rotated into proper placement, the mesentery attaches to the posterior abdominal wall.

Hindgut

The GI components of the hindgut include the left one-third of the transverse colon, the descending colon, ascending colon, sigmoid colon, rectum, and superior portion of the anal canal. Blood is supplied from the inferior mesenteric artery. The major developmental changes occur in the terminal hindgut known as the cloaca and involve formation of the anus. The hindgut initially ends at the cloacal membrane, which separates it from the anal pit or proctodeum. Around the fourth week of gestation, the urorectal septum forms and by the sixth week divides the cloaca into a ventral urogenital sinus and a dorsal anorectal canal.

By the eighth week of gestation, the anal membrane has moved inferior and is found at the bottom of the proctodeum. In the ninth week, this membrane ruptures, completing the patency of the GI tract.

PHYSIOLOGY OF THE GI TRACT

The GI system depends on the coordinated efforts of several organs for normal function. These organs include the oropharynx, esophagus, stomach, small intestine, liver, gallbladder, pancreas, large intestine, rectum, and anus.

The two main functions of the GI tract are digestion and absorption of nutrients and fluids, as well as elimination. Digestion is the process by which macronutrients (carbohydrates, fats, proteins) and micronutrients are broken down to an extent such that they can be absorbed into the bloodstream. Absorption is the process by which products of digestion travel across the cells and paracellular spaces lining the GI tract, and ultimately into the vascular or lymphatic circulation. Solids, liquids, and any materials that are not absorbed are passed out of the body through the process of elimination.

Digestive, absorptive, and elimination functions are supplanted by motility and secretory functions of the GI tract. The layers of the GI tract starting from the inner luminal side to the outermost layer include mucosa, submucosa, muscularis, and serosa. The mucosa includes epithelial enterocytes that directly participate in digestion and absorption. The muscularis layer is comprised of circular and longitudinal smooth muscles that carry out motility functions of the GI tract. Myenteric and submucosal plexuses are found within the muscularis layer and submucosal layer, respectively. These plexuses are the control center of the GI nervous system and help regulate sensory, motility, and secretory functions. In addition to the network of neurons that make up the enteric nervous system, the central nervous system can also process signals coming from the intestines as well as provide signals that affect the activity of the GI tract.

There remains much to be learned about the motility functions of the GI tract. GI motility has two main functions. The first is propulsion or peristalsis, which moves liquid and solid material along different parts of the tract. Motility also contributes to mechanical breakdown and mixing of solid materials that makes food particles more accessible for digestion by digestive juices and enzymes. It is believed that the interstitial cells of Cajal, which is part of the intrinsic GI nervous system, play an essential role in regulating motility by acting as the pacemaker cells of the GI tract. The pacemaker function of the interstitial cells of Cajal are analogous to the pacemaker functions of the sinoatrial node of the heart.

The function of the GI tract is closely regulated by a complex interplay of various hormones. Some of these hormones can be classified by their endocrine, neurocrine, or paracrine functions (Barrett, 2014). Endocrine hormones include gastrin, cholecystokinin, motilin, secretin, ghrelin, and glucose-dependent insulinotropic peptide. Neurocrine hormones include acetylcholine, vasoactive intestinal polypeptide, substance P, nitric oxide, cholecystokinin, 5-hydroxytryptamine, somatostatin, and calcitonin gene–related peptide. Examples of paracrine hormones include histamine, prostaglandins, somatostatin, and 5-hydroxytryptamine (Table 8.1).

Oral Pharynx

In children and adults, digestion begins in the mouth with the act of chewing. Digestion of a small percentage of carbohydrates begins in the mouth by the actions of salivary amylase from the parotid glands (Hall & Guyton, 2016). Since infants are edentulous and rely largely on breast milk or formula feedings, chewing does not play an important role in digestion for infants. However, the act of sucking and swallowing effectively and safely requires a complex orchestration between the central and peripheral nervous systems and oropharyngeal musculature. Dysfunction of any of these

TABLE 8.1

SUMMARY OF SELECT HORMONES AND CHEMICALS THAT AFFECT GASTRIC FUNCTION

Product	Source	Functions
Hydrochloric acid	Parietal cell	Digestion by hydrolysis, immunologic by sterilization of meal
Intrinsic factor	Parietal cell	Vitamin B_{12} transport and absorption
Pepsinogen	Chief cell	Initial protein digestion
Mucus, bicarbonate	Surface mucus cell; production stimulated by prostaglandin	Protection of gastric mucosa from acid injury
Histamine	Enterochromaffin cells	Regulate gastric secretion
Gastrin	G cells in gastric antrum, duodenum, and pancreas	Regulate gastric secretion
Gastrin-releasing peptide	Nerves	Regulate gastric secretion
Acetylcholine	Neurotransmitter at neural junctions	Regulates gastric secretion
Somatostatin	Delta cells found in pyloric antrum, duodenum, pancreatic islet cells	Multiple systemic functions including suppression of gastrointestinal hormones (gastrin, cholecystokinin, secretin, motilin, gastric inhibitory polypeptide, vasoactive intestinal peptide)

Source: Adapted from Barrett, K. E. (2014). *Gastrointestinal physiology*. New York, NY: McGraw-Hill.

structures may result in reduced or unsafe oral intake. Saliva produced by various glands serves an important role in the lubrication of the oral and esophageal mucosa, thereby facilitating comfortable passage of materials through the oral cavity and esophagus.

Swallowing is the first step in digesting and absorbing ingested fluids and solids. Swallowing begins when liquid or solid substances are detected by sensory nerves in the pharynx. These sensory impulses are transmitted via the trigeminal and glossopharyngeal nerves to the swallowing center in the brain, where the signals are processed. The swallowing center in turn coordinates muscle function by sending motor impulses to the pharynx and upper esophagus via cranial nerves 5, 9, 10, and 12 (Hall & Guyton, 2016). Breathing is inhibited during the process of swallowing to prevent aspiration of materials into the respiratory tract. Congenital or acquired dysfunction of the neural or muscular architecture involved in the swallowing process can lead to transient or chronic feeding problems.

Esophagus

The esophagus serves as a conduit for liquids and solids from the mouth to the stomach. It has autonomic motor activity that generates esophageal peristalsis sufficient to propel solids and liquids throughout its length (Hall & Guyton, 2016). Upper and lower esophageal sphincters regulate entry into the esophagus and stomach. Inappropriately high or low pressures generated at the lower esophageal sphincter can result in pathologic conditions such as achalasia or GER disease, respectively.

Stomach

The stomach is where a significant part of digestion begins. Gastric acid produced by parietal cells contributes to the digestive process along with gastric enzymes such as pepsinogen, which begins the breakdown of proteins. Parietal cells also produce intrinsic factor that plays a central role in the absorption of vitamin B_{12} in the terminal ileum. Even in patients who are treated for acid-related conditions, the physiologic importance of acid in digestion and defense against infectious agents needs to be recognized.

In addition to chemical and enzymatic digestion, the intrinsic motor activity of the stomach generates mechanical forces that churn, grind, and mix fluids and solids. These actions contribute to the process of physically breaking down foods to smaller particles. This mechanical breakdown increases the surface area of food boluses, making it more accessible for subsequent chemical and enzymatic digestion. In addition to regulating the rate at which fluids move from the stomach into the small intestine, the pyloric sphincter muscle helps ensure that food particles exiting the stomach are small enough to be acted on by the digestive enzymes and juices of the small intestine. Abnormalities in the neuromuscular function of the stomach can alter gastric motility, which may result in delayed gastric emptying. Delayed gastric emptying plays a role in other GI conditions such as GER and feeding problems.

The lining of the stomach is normally protected from the acidic environment by a mucus layer formed by mucinous film overlying the gastric mucosa. Sandwiched in between this mucus layer and gastric mucosa is a microenvironment containing bicarbonate ions. The mucinous film serves as the first line of defense against acid injury. Any acid that is able to penetrate this layer is neutralized in the bicarbonate microenvironment. Prostaglandins, leukotrienes, and thromboxane are chemical compounds produced by the arachidonic acid pathway. Collectively, these compounds participate in the regulation of numerous physiologic functions including thrombosis, inflammation, temperature regulation, and production of the mucinous layer that protects the stomach. Nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen are effective in treating fever, pain, and inflammation by blocking enzymes in the arachidonic acid pathway. While the antipyretic and analgesic affects are desired, the collateral reduction on prostaglandin synthesis also reduces the production of the mucosa layer, predisposing the gastric mucosa to acid injury.

Small Intestine

The small intestine is the site of absorption for the majority of liquids, macronutrients, and micronutrients. Digestion continues in the small intestine as the food bolus exiting the stomach is exposed to additional digestive enzymes and secretions from the hepatobiliary system and pancreas.

The liver performs many important metabolic functions that affect all other organ systems. Examples of these functions range from the metabolism of carbohydrate, fats, and proteins to the metabolism of medications. Another key function of the liver is the production of bile. After it is produced in hepatocytes, bile must make its way through the hepatobiliary duct system, which terminates in the first portion of the duodenum. Once it enters the duodenal lumen, bile serves an essential role in the transport of fats and fat-soluble vitamins to the surface of enterocytes, where they are subsequently absorbed. Smaller fat molecules can diffuse across the enterocyte membrane, while larger fat molecules require dedicated transmembrane transporters. Abnormalities in the production, processing, or flow of bile can result in a variety of congenital hepatobiliary abnormalities. Hepatobiliary diseases most often present with jaundice and failure to thrive due to malabsorption. Depending on the stage of the condition, the size of the liver and spleen may be variable. Reabsorption of bile acids in the terminal ileum followed by hepatic recycling accounts for over 90% of the bile pool.

Pancreatic exocrine function produces various enzymes including lipases, amylases, and peptidases that are responsible for breaking down fats, carbohydrates, and proteins, respectively. The pancreas also produces bicarbonate, which neutralizes acid coming from the stomach, protecting the intestinal mucosa from acid-associated injury. At the enterocyte surface, disaccharidases further break down carbohydrates into monosaccharides that can then enter the cell via dedicated transmembrane transport proteins. Amino acids, dipeptides, and tripeptides also use dedicated membrane transporters for absorption into enterocytes. Congenital or acquired causes that affect the architecture or function of these enterocyte surface enzymes can result in malabsorption.

The absorption of water is mainly driven by osmotic gradients that are initially established by the absorption of sodium and glucose. Water is absorbed by following the osmotic gradient through transmembrane and paracellular transport proteins. This mechanism helps explain the basis for including glucose and salts in commercial rehydration solutions.

Colon

The function of the colon is threefold: (1) maintenance of fluid and electrolyte balance, (2) formation of fecal matter, and (3) defecation.

The colon provides the body its last opportunity to reabsorb water and electrolytes. This process helps maintain fluid and electrolyte homeostasis, and serves to concentrate and solidify colonic luminal contents, culminating in stool formation. The major electrolytes included in this process are sodium, potassium, chloride, hydrogen, and bicarbonate. Transmembrane proteins on the apical and basolateral colonic cell surfaces facilitate the movement of electrolytes. Electrolyte movement, in turn, establishes electrochemical gradients that become the driving force for water resorption or secretion. Conditions in which the function of electrolyte transport mechanisms or colonic anatomy is compromised can clinically result in profuse diarrhea, as well as water and electrolyte imbalance.

The process of defecation requires coordination between the local enteric nervous system, central nervous system, abdominal musculature, internal anal sphincter, and external anal sphincter. In healthy individuals, the urge to defecate begins after a fecal bolus in the rectum accumulates and enlarges to a threshold size that leads to activation of mechanical stretch receptors. Activation of these mechanical receptors triggers a reflex relaxation of the internal anal sphincter. At the appropriate moment, under the individual's own volition, the external anal sphincter is relaxed. Coordination of external anal sphincter relaxation with an increase in intra-abdominal pressure from contraction of abdominal muscles facilitates the expulsion of stool.

Congenital or acquired conditions that result in the dysfunction of any of the neurologic or muscular processes can lead to disorders of defecation. Hirschsprung's disease (HD) is an example where dysfunction in local neuromuscular control mechanisms results in the inability to evacuate stool normally. The complexity of the coordination needed for normal defecation helps to explain the seemingly monumental effort infants exhibit in straining when they defecate.

Genetic Syndromes. A syndrome is a group of signs or symptoms that consistently occur together, or a condition characterized by a set of associated symptoms. Many syndromes occur because of a genetic or chromosomal abnormality. Humans have 23 pairs of chromosomes, or 46 in all. Babies with chromosomal conditions have a problem in one or more of their chromosomes. Chromosomes comprise mainly of DNA, the instructions for making proteins, and genes, the building blocks of heredity. Proteins serve essential structural and functional roles throughout the body, but sometimes a mutation—a change in a gene or genes—alters the gene's instructions for making a protein such that the protein does not function properly or is missing entirely. These mutations are the basis of genetic disorders. Because one chromosome in each pair comes from the mother and the other from the father, inherited gene mutations can be from one or both parents. Abnormal genes or chromosomes may result in structural or functional abnormalities in the GI tract as well as other systems. Table 8.2 is a summary of selected syndromes associated with GI abnormalities.

Diagnostic Modalities. The care of neonates has vastly improved with advances in technology. However, many neonates can be evaluated using simple and noninvasive diagnostic modalities. The following spectrum of diagnostic modalities is usually available in centers with neonatal intensive care units for the management of GI problems.

Nasogastric Tube

Nasogastric (NG) tube placement can be used for diagnostic purposes in two situations. The first is to check for patency of the nares and esophagus if anatomic anomalies are suspected. If an esophageal anatomic anomaly is present, the NG tube cannot be advanced into the stomach as evident by plain radiography. A second diagnostic application of NG tube is collection of a gastric aspirate sample. A gastric aspirate sample may be necessary to check for the presence of blood and to determine the blood's origin (infant or mother, via the Apt test). A gastric aspirate sample may also be used to check the gastric pH to guide acid suppression therapy; the normal gastric pH is less than 2, and effective acid suppression is achieved if the pH is greater than 4.

If an NG tube is required for diagnostic purposes, usually a 4 French tube is inserted through the nares (or the oral cavity in some cases) and advanced to a premeasured length.

Stool Studies

Stool is an excretory product of the GI tract composed of GI secretions, bile and pancreatic fluid, undigested/unabsorbed food, and microbes. Stool examination is helpful in identifying the presence and possible causes of GI pathology.

Basic clinical observations and examination of stool can yield important initial diagnostic clues. Timing of the passage of the first meconium stool should be noted, as delayed passage of meconium (beyond 24 hours) is suggestive of a lower colonic obstruction like

TABLE 8.2

COMPARISON OF GASTROINTESTINAL MANIFESTATIONS OF SELECTED GENETIC SYNDROMES

Syndrome	GI Problem	Cleft Lip/ Palate	Omphalocele	Malrotation	Imperforate Anus	Tracheoesophageal Fistula	Hirschsprung's Disease	Pyloric Stenosis	Duodenal Atresia	Liver Disease	Pancreatic Disease
Alagille	Cholestasis, intrahepatic biliary hypoplasia									X	
Apert	Cleft/narrow palate, pyloric stenosis, anterior/ectopic anus	X						X			
Beckwith–Weidemann	Macroglossia, omphalocele		X								
Fetal Hydantoin	Cleft lip and palate, pyloric stenosis, duodenal atresia, imperforate anus	X			X			X	X		
Fetal Valproate	Cleft lip and palate	X									
Meckel–Gruber	Cleft palate and/or lip, omphalocele, malrotation, imperforate anus	X	X	X	X						
Sirenomelia (mermaid malformation)	Esophageal atresia, imperforate anus, tracheoesophageal fistula				X	X					
Trisomy 13	Cleft lip/palate, omphalocele, malrotation	X	X	X							
Trisomy 18	Cleft lip/palate, pyloric stenosis, omphalocele, malrotation, biliary atresia	X	X	X				X		X	

(*continued*)

TABLE 8.2

COMPARISON OF GASTROINTESTINAL MANIFESTATIONS OF SELECTED GENETIC SYNDROMES (*continued*)

Syndrome	GI Problem	Cleft Lip/ Palate	Omphalocele	Malrotation	Imperforate Anus	Tracheoesophageal Fistula	Hirschsprung's Disease	Pyloric Stenosis	Duodenal Atresia	Liver Disease	Pancreatic Disease
Trisomy 21	Tracheoesophageal fistula, duodenal atresia, annular pancreas, Hirschsprung's disease, imperforate anus				X	X	X		X		X
Waardenburg	Hirschsprung's disease						X				
Brandt syndrome—zinc deficiency	Chronic diarrhea										
Heterotaxy	Agenesis of dorsal pancreas										X
Mowat–Wilson	Hirschsprung's disease						X				
Johanson–Blizzard	Exocrine pancreatic insufficiency										X
Wolf Hirschhorn	Cleft lip/palate	X									
Wolman disease	Liver failure, hepatomegaly									X	
Zellweger	Hepatomegaly									X	
Di George	Cleft palate	X									
Cornelia de Lange	Cleft palate	X									

HD or anorectal malformation. Stool color results from bile that is altered by colonic bacteria; normal stool color is yellow to brown. Green stool is usually seen in patients with diarrhea (rapid transit). Bright red stool implies possible bleeding from the colon or anus, while dark red, maroon, or black stool suggests that the source of blood is in the small bowel or stomach. Lighter colored (acholic) or pale stool implies decreased bile in the bowel as seen in patients with biliary obstruction (biliary atresia) or cholestasis.

Several stool tests can help as screening tests for GI tract pathology. Occult blood and white blood cells (eosinophils) are present in patients with cow or soy milk-induced allergic colitis. A stool pH of less than 5.5 is seen in carbohydrate or fat malabsorption. The presence of more than one reducing substance is suggestive of carbohydrate (except sucrose) malabsorption. Stool calprotectin and lactoferrin are used as markers of inflammation in the GI tract. Their usefulness as screening markers in infants with enterocolitis (necrotizing enterocolitis, NEC, or allergic) is under investigation (Nakayuenyongsuk et al., 2018; Pergialiotis et al., 2016).

Stool cultures test for bacterial pathogens in cases of diarrhea. In neonates, stool should not be routinely tested for the *Clostridium difficile* toxin, as healthy neonates can become colonized by *C. difficile* in the first few days of life (Lees, Miyajima, Pirmohamed, & Carrol, 2016).

Fecal elastase 1 (FE1) is a useful marker of exocrine pancreatic function (Lüth et al., 2001). FE1 is usually low in meconium and reaches normal levels by day 3 in term newborns and by 2 weeks in infants born before 28 weeks of gestation. The FE1 level is a useful adjunct diagnostic test for pancreatic insufficiency in patients suspected of having cystic fibrosis (CF).

Radiologic Studies

Radiologic studies of the GI tract are performed to look for anatomic abnormalities, obstruction, or perforation in babies presenting with vomiting, abdominal distension, constipation, or a catastrophic illness like shock. The GI tract is filled with fluid at birth, but as the infant swallows air after delivery, air travels through the gut rapidly, filling the stomach within 30 minutes and reaching the distal small bowel by 4 hours and rectum by 6 to 8 hours. In cases of obstruction, the portion of the intestine distal to the obstruction remains airless and the portion of the intestine proximal to the obstruction becomes dilated. As the infant continues to swallow air, the proximal intestine may become very dilated, causing a large bubble-like appearance on plain radiographs.

Plain radiographs of the chest and abdomen in a supine or upright position are a very useful initial diagnostic modality in patients with suspected GI tract obstruction. The absence of air in the stomach is suggestive of esophageal atresia. A dilated stomach in conjunction with the absence of air in the small intestine is suggestive of duodenal obstruction. The absence of rectal air is suggestive of intestinal obstruction; cross-table lateral plain radiographs may be more helpful to look for air in the rectum. A left lateral decubitus plain radiograph is recommended to look for free intraperitoneal air if perforation is suspected.

An upper GI series is performed using contrast (barium or Gastrografin) that is either swallowed or delivered by a NG tube before a series of radiographs are taken. An upper GI series can be considered in babies who present with vomiting, abdominal distension, or poor growth. Results of an upper GI series may be diagnostic for pyloric stenosis, intestinal malrotation, or duodenal obstruction. An upper GI series often shows reflux of gastric contents back into the esophagus; however, the study cannot distinguish between physiologic versus pathologic reflux. In addition to diagnostic purposes, the upper GI contrast study can also be used to define anatomy prior to surgical intervention such as gastrostomy tube placement or fundoplication. The study usually requires the baby to be fasting for at least one feeding (4–6 hours), and the examination may last 30 minutes. A small bowel series examination may take up to 4 to 6 hours. In cases of suspected perforation, water-soluble contrast (Gastrografin) should be used.

Contrast enema examination is performed using barium or Gastrografin to evaluate the large intestine in suspected cases of malrotation, small left colon, HD, or obstruction by meconium plug. Contrast enema examination should be done prior to upper GI series, as contrast from the upper GI examination may take several days to clear. If a patient already has had an upper GI series, then a gentle saline enema may help clear contrast faster; otherwise, no special preparation is needed prior to contrast enema. A saline enema may be used after a contrast enema if the contrast is not cleared.

Ultrasonography is a noninvasive test that is the modality of choice for diagnosing pyloric stenosis or intestinal duplication cyst, and evaluating the gallbladder and extrahepatic biliary system. Doppler sonography may be used to diagnose portal vein thrombosis.

Nuclear medicine scan or scintigraphy is done by performing imaging after a radioactive tracer is ingested or injected intravenously. A gastric emptying scan uses technetium-tagged formula fed to the infant and may be used to detect aspiration (with swallowing or from gastric reflux) and measures gastric emptying time in patients with feeding intolerance. A Meckel's scan is performed by intravenous injection of Tc-99m pertechnetate, which avidly accumulates in gastric mucosa, and is the study of choice in patients suspected of having a Meckel's diverticulum causing lower GI bleeding. A hepatobiliary hydroxy iminodiacetic acid (HIDA) scan, also known as hepatobiliary scintigraphy, is performed by administering radioactive tracer intravenously and obtaining images over 4 hours and then 24 hours later. The HIDA scan is used to evaluate liver, gallbladder, and bile duct pathology. At some institutions, phenobarbital is given for 5 to 7 days prior to a HIDA scan to improve accuracy (Kwatra et al., 2013).

Esophageal pH Probe

An esophageal pH probe test is performed by placing a thin, flexible electrode with one or two pH sensors in the distal esophagus; data is collected by a portable recorder. After 24 to 48 hours, the probe is removed, and data are analyzed. The diagnosis of acidic GER depends on a complex scoring system based on the number of reflux episodes, the number of episodes greater than 5 minutes, the duration of longest episode, and, most importantly, the percentage of time in reflux. It can be used to diagnose GER. It is also used to document the association of any symptom with reflux; symptoms that may be associated with reflux include apnea, bradycardia, oxygen desaturation, cough, or irritability. Since formula neutralizes acid, this test has to be done while the patient is taking bolus feedings 3 hours apart. The patient must also be off any acid-suppressive and promotility treatment for 1 to 2 days preceding, and during the study period. In cases where an esophageal pH probe study has to be done while the patient is receiving continuous feeding, or acid-suppressive treatment cannot be stopped, the formula can be acidified by adding citric acid, or an impedance probe can be used. An impedance probe detects any reflux, acidic or alkaline, but it is thicker than a standard pH probe.

Endoscopy

Diagnostic and therapeutic endoscopy is now feasible even in micropreemies with the rapid evolution of fiber optics and digital imaging processors. Endoscopy can be performed at bedside; small babies may need to be intubated. Table 8.3 shows the common indications for endoscopy in infants.

TABLE 8.3

INDICATIONS FOR ENDOSCOPY

Upper Endoscopy	
Diagnostic Indication	**Entities Diagnosed**
Persistent vomiting without obstruction Hematemesis/upper gastrointestinal bleeding Chronic diarrhea	Esophagitis, gastritis, gastric mucosal hypertrophy, ulcer, small bowel villous abnormalities
Therapeutic Indications	**Procedure Performed**
Feeding problems Upper gastrointestinal bleeding Dysphagia Esophageal stricture (after TE fistula repair)	Percutaneous Endoscopic Gastrostomy (PEG) tube placement Control of bleeding Dilation of stricture
Colonoscopy	
Diagnostic Indications	**Entities Diagnosed**
Hematochezia Constipation	Colitis (allergic) Hirschsprung's disease (rectal biopsy)

TRACHEAL ESOPHAGEAL FISTULA AND ESOPHAGEAL ATRESIA

Background

Esophageal atresia (EA) is defined as a complete interruption in continuity of the esophagus. Tracheoesophageal fistula (TEF) is a pathologic connection between the esophagus and trachea. The five major types of TEF are summarized in Figure 8.1.

Other congenital anomalies that may be associated with EA and TEF include vertebral, intestinal atresia, anorectal malformations (ARM), cardiac, renal, and limb anomalies. VACTERL (vertebral, anorectal, cardiovascular, tracheoesophageal, renal, and limb anomalies) syndrome is diagnosed when three or more of these anomalies are present. Approximately 19% of babies with EA and TEF have VACTERL syndrome (Bruch, Kunisaki, & Coran, 2016). Five percent of these neonates will also have chromosomal anomalies such as trisomy 13, 18, and 21. Other conditions that may be associated with EA and TEF include CHARGE (coloboma, heart defect, atresia choanae, retarded growth and development, genital abnormality, and ear abnormality) syndrome, Potter's syndrome, and pyloric stenosis (Bruch et al., 2016).

The survival rate of infants with EA with or without TEF based on birth weight (BW) and cardiac anomalies has been studied. Infants with no cardiac anomalies and a BW of greater than 2,000 g have a 100% survival rate, while infants with a BW of less than 2,000 g were found to have an 82% survival rate. Infants with a major cardiac anomaly and a BW of greater than 2,000 g have a 72% survival rate, while infants with a BW of less than 2,000 g had a survival rate of 27% (Bruch et al., 2016; Okamoto et al., 2009).

Diagnosis

Most neonates with EA and TEF present soon after birth with difficulty swallowing even their normal production of saliva. The swallowing problems can result in choking, coughing, gagging, and/or cyanosis, particularly during feedings. Difficulty with advancing a NG tube should raise suspicion of esophageal pathology, and be followed by a plain radiograph that includes views of the neck, chest, and abdomen. Coiling of the NG tube tip in the vicinity of the proximal esophagus supports the diagnosis of EA. Absence of bowel gas on plain abdominal radiograph is suggestive of EA without a distal fistula, while the presence of gas throughout the small and large bowel suggest a distal TEF. Further mapping of a proximal fistula can be done by radiographic contrast study or rigid bronchoscopy depending on institutional availability. Neonates who have TEF without EA (H-Type) may present beyond the newborn period (Bruch et al., 2016). In these babies, a NG tube may terminate in the stomach, but the baby will have persistent coughing and choking with feeds.

Additional findings may be associated with EA and TEF. Limb and anorectal anomalies may be observed on physical examination. Vertebral anomalies can be detected by plain radiography. Abdominal ultrasonography and echocardiogram may reveal renal abnormalities or a tethered spinal cord, and cardiac anomalies, respectively.

Management

Management should be in collaboration with a pediatric surgery team. Prior to surgery, steps should be taken to minimize the risk of oral pulmonary aspiration. The neonate should be placed supine with the head elevated at a 30° to 45° angle. An oral or nasal esophageal tube should be placed for continuous low suction. Oral secretions can be thick and sticky, causing frequent clogging of the suction tubing. Thus, tubes may need to be routinely flushed or changed. **Quality and Safety: Patency of the tube should be checked if symptoms of increased choking, gagging, or respiratory problems arise. Intravenous broad-spectrum antibiotics should also be started.** Specific details on the variations in surgical approaches have been well described (Bruch et al., 2016; van der Zee, Tytgat, & van Herwaarden, 2017).

Postoperatively, the baby should be managed with parenteral nutrition (PN), antibiotics, and acid suppression. Anastomoses site leakage can be a complication after surgery, and should be considered if there are acute clinical or vital sign changes. If a chest tube is in place, anastomoses site leakage may present as persistent or increased drainage. Frequent oropharyngeal suctioning and elevating the head of the bed will reduce the risk of aspiration. For oral suctioning, the catheter should be inserted to a predetermined depth that is well above the surgical site to avoid any potential trauma. The timing and initiation of gastric feedings should be determined in collaboration with the surgical team. An esophagram on postoperative days 5 to 7 can be considered to look for anastomotic leaks prior to starting oral feedings. Infants who have a gastrostomy tube or a transanastomotic tube ending in the stomach can be fed 2 to 3 days after surgical repair (Bruch et al., 2016).

Postoperative complications may include GER (40%–70%), anastomoses site leak (17%), anastomosis site stricture (40%–50%), fistula recurrence (5%–12%), and esophageal dysmotility (75%–100%; Berseth & Poenaru, 2005; Kovesi & Rubin, 2004).

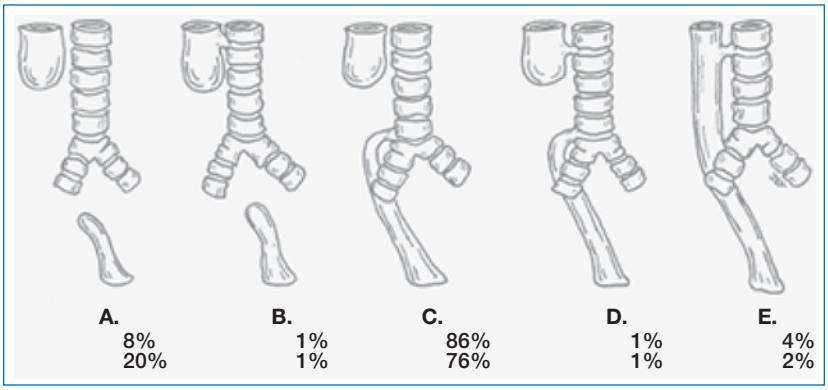

FIGURE 8.1 Diagram of the main types of esophageal atresia (EA) with or without a tracheoesophageal fistula (TEF). Type A is EA without a TEF and is often called pure EA. Shown are the blind upper and lower esophageal pouches next to the ringed windpipe (trachea) and the branches (bronchi) that lead to each lung. Type B has a connection (fistula) between the upper pouch and the trachea (a TEF). Type C is by far the most common form of EA and has a fistula between the lower esophagus and the trachea (one form of TEF) with a blind upper pouch. A rare form (1%) is type D with two TEFs, one between both the upper and lower esophageal segments and the trachea. Type E has only a TEF and no EA. This is usually referred to as an H- or N-shaped fistula and may be 2% to 4% of this group. The H-fistulas are divided surgically, and nothing further needs to be done to the esophagus, which is intact and reaches normally to the stomach.

GASTROESOPHAGEAL REFLUX

Background

GER is defined as the passage of gastric contents into the esophagus with or without regurgitation and vomiting (Rosen et al., 2018). In contrast, gastroesophageal reflux disease (GERD) is when GER leads to troublesome symptoms that affect daily functioning and/or result in complications (Rosen et al., 2018). Table 8.4 lists some of the symptoms and signs that may suggest GERD. It is often a challenge to distinguish between GER and GERD in infants, as there is no consistently reliable test that has been routinely recommended to diagnose GER/GERD (Rosen et al., 2018). The diagnosis therefore most often relies on clinical judgment. Since the common symptoms of GER are nonspecific, conditions other than GER should also be considered in evaluating any infant (Table 8.5).

Most episodes of GER are normal or physiologic, and usually go unnoticed. The precise prevalence of GER and GERD in infants is unclear. Based on esophageal pH monitoring studies, healthy infants may have up to 31 episodes of gastroesophageal acid reflux a day (Vandenplas, Goyvaerts, & Helven, 1991). The same study suggests that less than 10% of infants and children have GERD.

Three physiologic strategies limit GER and the development of GERD (Vandenplas & Hassall, 2002). First is the anatomic antireflux barrier that comprises the lower esophageal sphincter (LES), the diaphragmatic pinchcock, and the angle of His. These anatomic structures form a physical barrier that limits the frequency and severity of GER events. It is thought that inappropriate transient lower esophageal sphincter relaxation (TLESR) is the primary factor responsible for GER. The second physiologic strategy that limits the complications of GER is esophageal peristalsis and clearance, which removes any gastric content that enters the esophagus as a result of GER. Third is the epithelial layer architecture, including a protective mucous layer and tight epithelial cell junctions, which helps to reduce the esophageal injury that can result from contact with gastric contents. Compromise of one or more of these defense strategies can result in the symptoms or complications of GERD (Vandenplas & Hassall, 2002).

TABLE 8.4

CLINICAL PRESENTATION THAT MAY SUGGEST GERD

Symptoms	Signs
General	
• Persistent crying or irritability • Poor growth • Dystonic head posturing (Sandifer syndrome) • Sleeping problems	• Anemia
Gastrointestinal	
• Recurrent regurgitation • Hematemesis • Dysphagia • Feeding difficulties	• Esophagitis
Airway	
• Wheezing • Stridor • Cough • Hoarseness • Asthma refractory to therapy	• Apnea • Brief resolved unexplained events • Aspiration pneumonia • Recurrent pneumonias

GERD, gastroesophageal reflux disease;

Source: Adapted from Rosen, R., Vandenplas, Y., Singendonk, M., Cabana, M., DiLorenzo, C., Gottrand, F., . . . Tabbers, M. (2018). Pediatric gastroesophageal reflux clinical practice guidelines: Joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *Journal of Pediatric Gastroenterology and Nutrition, 66*(3), 516–554. doi:10.1097/MPG.0000000000001889

TABLE 8.5

DIFFERENTIAL DIAGNOSIS OF GERD IN NEONATES AND INFANTS

Gastrointestinal obstruction • Pyloric stenosis • Malrotation with volvulus • Hirschsprung's disease • Antral/duodenal web • Abdominal tumor/mass	**Other gastrointestinal disorders** • Achalasia • Gastroparesis • Peptic ulcer disease • Eosinophilic gastroenteritis • Food allergy/intolerance • Pancreatitis • Cholelithiasis/cholecystitis
Neurologic • Hydrocephalus • Subdural hematoma • Intracranial hemorrhage • Intracranial mass	**Infectious** • Sepsis/meningitis • Urinary tract infection • Upper/lower airway infection • Otitis media • Hepatitis
Cardiac • Heart failure	**Renal** • Obstructive uropathy • Renal insufficiency
Metabolic/endocrine • Galactosemia • Hereditary fructose intolerance • Urea cycle defects • Amino and organic acidemias • Metabolic acidosis • Congenital adrenal hyperplasia/adrenal crisis	• Pediatric condition falsification disorder by proxy • Child neglect or abuse • Vascular ring • Autonomic dysfunction

GERD, gastroesophageal reflux disease.

Source: Adapted from Rosen, R., Vandenplas, Y., Singendonk, M., Cabana, M., DiLorenzo, C., Gottrand, F., . . . Tabbers, M. (2018). Pediatric gastroesophageal reflux clinical practice guidelines: Joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *Journal of Pediatric Gastroenterology and Nutrition, 66*(3), 516–554. doi:10.1097/MPG.0000000000001889

TABLE 8.6

KEY HISTORY QUESTIONS IN EVALUATING INFANT GER/GERD

Feeding and diet history	• Duration of each feeding • Interval between feedings • Volume of each feed • Current and past formula(s) used • Method for mixing formula • Maternal diet history if infant using breast milk
Pattern of regurgitation, spitting up, or vomiting	• Nocturnal • Immediately post prandial • Long after meals • Undigested versus digested • Presence of red or brown material to suggest hematemesis
Family medical history	• Food allergies/intolerance • Environmental allergies • Asthma • Gastrointestinal problems • Metabolic or neurologic conditions
Social history	• Family psychosocial stressors • Mood and affect of caretakers • Exposure to tobacco
Medical history	• Concurrent medical problems • Other symptoms and signs, including red flags • Growth chart parameters—weight, length, head circumference

GER, gastroesophageal reflux; GERD, gastroesophageal reflux disease.

Source: Adapted from Rosen, R., Vandenplas, Y., Singendonk, M., Cabana, M., DiLorenzo, C., Gottrand, F., . . . Tabbers, M. (2018). Pediatric gastroesophageal reflux clinical practice guidelines: Joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *Journal of Pediatric Gastroenterology and Nutrition, 66*(3), 516–554. doi:10.1097/MPG.0000000000001889

Diagnosis

For most infants with recurrent regurgitation or spitting up, a detailed history (Table 8.6) and physical examination with attention to warning symptoms and signs (Table 8.7) that may suggest other causes is typically sufficient to make a clinical diagnosis of uncomplicated GER (Rosen et al., 2018). Neonates and infants in the hospital setting with GERD may pose a greater diagnostic challenge, as some of the symptoms and signs may be nonesophageal. Examples include apnea, bradycardia, and cyanosis during or unrelated to feedings.

Despite the frequency with which nonesophageal symptoms such as irritability and apnea trigger further investigation for or treatment of GER/GERD, a clear cause and effect relationship has not been well established (Abu Jawdeh & Martin, 2013; Heine, Jordan, Lubitz, Meehan, & Catto-Smith, 2006; Ramaiah, Stevenson, & McCallion, 2005; Zimbric, Bonkowsky, Jackson, Maloney, & Srivastava, 2012). Indeed, while proton pump inhibitors (PPIs) are the most effective acid suppression agents, several well-conducted studies in infants have not shown PPIs to be of benefit in reducing clinical symptoms (Davidson et al., 2013; Orenstein, Hassall, Furmaga-Jablonska, Atkinson, & Raanan, 2009; Writing Committee for the American Lung Association Asthma Clinical Research Centers, 2012).

Some infants who have symptoms of GER/GERD may require additional testing. However, there are no clear indications as to when further testing may be helpful. Broad guidelines for when to consider testing may include infants who have GER before the age of 1 week, infants who have red flag signs or symptoms, and infants with unexplained extraesophageal manifestations that may be related to GER (Rosen et al., 2018; see Table 8.7). Particular areas of ongoing controversy include the relationship of GER and respiratory disorders, and the relationship between GER and distressed behaviors in infants (Abu Jawdeh & Martin, 2013; Zimbric et al., 2012).

The current battery of tests available to evaluate for GER/GERD is outlined in Table 8.8. Routine testing beyond a thorough history and physical examination is typically not recommended unless red flag symptoms or signs are present (Rosen et al., 2018).

The 24 to 48 hour esophageal pH monitoring test with or without impedance is currently the only testing modality that enables correlation of intraesophageal events with clinical symptoms (Salvatore & Vandenplas, 2016). The test involves inserting a nasal esophageal catheter that remains in place for 24 to 48 hours. In the case

TABLE 8.7

RED FLAG SYMPTOMS AND SIGNS THAT SUGGEST DISORDERS OTHER THAN GERD

Symptoms and Signs	Comments
General • Weight loss or inappropriate weight gain • Lethargy • Fever • Excessive irritability/pain • Change in character or quantity of urine	• Suggesting various conditions, including systemic infections • May suggest urinary tract infection
Neurologic • Bulging fontanel/rapidly increasing head circumference • Seizures • Macrocephaly/microcephaly • Lethargy	• May suggest increased intracranial pressure—e.g., meningitis, brain tumor, or hydrocephalus
Gastrointestinal • Persistent forceful vomiting • Vomiting not associated with feedings • Bilious vomiting • Hematemesis • Chronic diarrhea • Rectal bleeding • Abdominal distension	• May suggest hypertrophic pyloric stenosis • May suggest increased intracranial pressure • Regarded as symptom of intestinal obstruction. Possible causes: Hirschsprung's disease, intestinal atresia, or midgut volvulus or intussusception • Suggests a potentially serious bleed from the esophagus, stomach, or upper GI tract, possibly GERD-associated, occurring from acid peptic disease, Mallory–Weiss tear, or reflux esophagitis • Indicative of obstruction, dysmotility, or anatomic abnormalities

GERD, gastroesophageal reflux disease; GI, gastrointestinal.

Source: Adapted from Rosen, R., Vandenplas, Y., Singendonk, M., Cabana, M., DiLorenzo, C., Gottrand, F., . . . Tabbers, M. (2018). Pediatric gastroesophageal reflux clinical practice guidelines: Joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *Journal of Pediatric Gastroenterology and Nutrition, 66*(3), 516–554. doi:10.1097/MPG.0000000000001889

TABLE 8.8

SELECTED STUDIES TO CONSIDER IN NEONATES AND INFANTS WITH SUSPECTED GERD

Study	What the Study Can Help Diagnose or Determine	Comments
Upper GI barium contrast	• Anatomic abnormalities of the esophagus, stomach, and upper small bowel • E.g., gastric outlet obstruction, small bowel obstruction, small bowel malrotation and volvulus, pyloric stenosis, esophageal stricture, esophageal extrinsic compression, duodenal stenosis/web, hiatal hernia, tracheal esophageal fistula	• Insufficient evidence to support use of barium contrast study for the primary diagnosis of GERD
Ultrasound	• Pyloric stenosis, hydronephrosis, ureteropelvic obstruction, gallstones	• No evidence to support use of ultrasound for the diagnosis of GERD
EGD	• Acid-related esophagitis, eosinophilic esophagitis, peptic ulcer disease, gastritis, duodenitis, *Helicobacter pylori* • Hiatal hernia	• Insufficient evidence to support use of EGD for the diagnosis of GERD • Based on expert opinion, EGD with biopsies can be considered to assess complications of GERD when an underlying mucosal disease is suspected or prior to escalating therapy
Scintigraphy	• Delayed gastric emptying, gastroparesis	• Insufficient evidence to support use to establish a diagnosis of GERD

(*continued*)

TABLE 8.8

SELECTED STUDIES TO CONSIDER IN NEONATES AND INFANTS WITH SUSPECTED GERD (*continued*)

Study	What the Study Can Help Diagnose or Determine	Comments
PPI trial	• Five trials in preterm and full-term infants show reduction in symptoms	• No evidence to support empiric trial of PPI for the diagnosis of GERD in infants
24- to 48–hour esophageal pH with or without impedance monitoring	• Correlation of GER episodes with clinical symptoms and signs (e.g., apnea, bradypnea, bradycardia, spitting up, cough, irritability) • Detection of acid- (pH) and nonacid- (impedance) related GER episodes • Efficacy of acid suppression therapy	• Insufficient evidence to support the routine use of pH and/or impedance monitoring for the diagnosis of GER in infants and children

EGD, esophagogastroduodenoscopy; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor.

Source: Adapted from Rosen, R., Vandenplas, Y., Singendonk, M., Cabana, M., DiLorenzo, C., Gottrand, F., . . . Tabbers, M. (2018). Pediatric gastroesophageal reflux clinical practice guidelines: Joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *Journal of Pediatric Gastroenterology and Nutrition, 66*(3), 516–554. doi:10.1097/MPG.0000000000001889

of pH monitoring, the catheter has sensors that detect changes in pH. The advantage of a dual pH/impedance catheter is that impedance sensors will detect any movement of air or liquid, regardless of pH. Thus, GER that is nonacidic will also be detected (Salvatore & Vandenplas, 2016). Since both acidic and nonacidic refluxate may contribute to clinical symptoms, dual monitoring may offer additional helpful information compared to pH monitoring alone.

Management

Beyond regurgitation and vomiting, the symptoms often attributed to GER/GERD are nonspecific and insensitive for establishing a diagnosis. This diagnostic uncertainty makes the decision whether to treat and how to treat GER/GERD equally challenging. Treatment options can be divided into pharmacologic and nonpharmacologic approaches.

Nonpharmacologic strategies should be considered in most infants with GER/GERD (Craig, Hanlon-Dearman, Sinclair, Taback, & Moffatt, 2004; Horvath, Dziechciarz, & Szajewska, 2008; Vandenplas & Sacre, 1987). Nonpharmacologic approaches include thickening feeds, modifying feeding volumes, elimination of cow's milk protein, and position changes (Bautista, Fullerton, Briseno, Cui, & Fass, 2004; Rosen et al., 2018; see Table 8.9). Despite the possible benefits to positioning in the treatment of GER, only the supine position is recommended by the National Health Service and the American Academy of Pediatrics as the safest position to reduce the risk of sudden infant death syndrome (SIDS; Moon, 2011).

Acid suppression therapy and prokinetic agents are two common medical management options. PPIs and histamine-2 receptor antagonists (H_2A) are the two most prescribed acid suppression agents. After reviewing the current evidence addressing the use of PPIs in infants, the GER guideline committee concluded that it is uncertain whether the use of PPIs or H_2As reduces crying/distress, visible vomiting/regurgitation, or signs and symptoms of GERD (Rosen et al., 2018). The working group subsequently recommended against the routine use of H_2A or PPI for the treatment of crying/distress or visible regurgitation in otherwise healthy infants. However, the same group determined that the current body of evidence does support the use of PPIs as first line for treating GERD-related erosive esophagitis (Rosen et al., 2018). Considering that few infants undergo endoscopy with biopsy, which is the gold standard for diagnosing erosive esophagitis related to GERD, clinicians are left with clinical symptoms as the main determinant whether acid suppression treatment is warranted.

If the decision is to proceed with treatment, a reasonable approach may be to begin with a time-limited trial with an H_2A agent. If there is no improvement in targeted symptoms, then a subsequent trial with a PPI can be considered. If target symptoms fail to improve or resolve with acid suppression therapy, the treatment should be discontinued. Practitioners should also be aware that while PPIs may effectively reduce esophageal acid reflux in neonates, they may not impact the symptoms associated with GERD (Davidson et al., 2013).

Prokinetic agents are a second class of drugs available to treat GER/GERD. Metoclopramide is one of the more commonly prescribed prokinetic agents in infants, although its effectiveness is far from satisfactory (Craig et al., 2004). Coupled with its unfavorable side effects profile including somnolence, irritability, galactorrhea, extrapyramidal reactions, and potentially permanent tardive dyskinesia, metoclopramide is not highly recommended in infants (Putnam, Orenstein, Wessel, & Stowe, 1992).

Over the past 10 years, there has been increasing use of erythromycin as prokinetic therapy. Erythromycin is an antibiotic that is also a motilin receptor agonist. Motilin is a physiologic hormone that increases GI motility when bound to the motilin receptor located throughout the GI tract. While there have not been sufficient studies for or against its effectiveness, there have been a limited number of studies to suggest that erythromycin ethylsuccinate (EES) may be helpful in some infants at reducing GER/GERD symptoms (Rosen et al., 2018).

For infants with GERD symptoms refractory to medical therapy, transpyloric tube feedings may be effective at improving feeding tolerance (Malcolm, Smith, Mears, Goldberg, & Cotten, 2009; Misra, Macwan, & Albert, 2007). Surgical intervention can be considered in rare cases in which medical management is not effective and the benefits of surgery outweigh the risks and potential long-term side effects (Rosen et al., 2018).

HYPERTROPHIC PYLORIC STENOSIS

Background

Hypertrophic pyloric stenosis (HPS) is the most common gastric surgical disorder in neonates (Seifarth & Soldes, 2016). HPS is characterized by progressive hypertrophy of the circular muscle that surrounds the gastric pylorus. The progressive hypertrophy culminates in a high-grade or complete gastric outlet obstruction (Seifarth & Soldes, 2016). The precise etiology and pathogenesis

TABLE 8.9

SUMMARY OF NONPHARMACOLOGIC OPTIONS FOR GER/GERD

Intervention	Comments	References
Thickened feedings	• May reduce observable regurgitation episodes, but may not affect the actual frequency of GER	Chao & Vandenplas, 2007; Corvaglia et al., 2006; Horvath et al., 2008; Iacono et al., 2002
Reducing feeding volumes	• Recommended based on expert opinion	• No RCT has looked at effects of reduced feeding volume
Elimination of cow's milk protein	• Some infants with cow's milk protein allergy may have regurgitation as their primary symptom • Trial of protein hydrolysate formula can be considered if CMPA is suspected (hematochezia, eczema, family history of allergic conditions) • Amino acid formulas should be reserved for infants with CMPA refractory to treatment with a protein hydrolysate formula	• No RCT specifically evaluating effects of eliminating CMP on GER • Some studies show reduced regurgitation in infants with CMPA treated with amino acid–based formula • For breastfed infants, eliminating cow's milk-containing products and beef from mother's diet can be considered
Positioning therapy	• Left lateral decubitus position may reduce total number of reflux episodes	Loots et al., 2014; Moon, 2011; Omari et al., 2004; Rosen et al., 2018

For each nonpharmacologic strategy, a minimum 2-week trial is recommended to assess for symptom improvement before considering other therapeutic options.

CMP(A), cow's milk protein (allergy); GER, gastroesophageal reflux; GERD, gastroesophageal reflux disease; RCT, randomized controlled trial.

Source: Adapted from Rosen, R., Vandenplas, Y., Singendonk, M., Cabana, M., DiLorenzo, C., Gottrand, F., . . . Tabbers, M. (2018). Pediatric gastroesophageal reflux clinical practice guidelines: Joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *Journal of Pediatric Gastroenterology and Nutrition, 66*(3), 516–554. doi:10.1097/MPG.0000000000001889

of HPS is unclear. Several factors are thought to play a role in the development of HPS. There seems to a genetic predisposition based on studies demonstrating familial aggregation, first-born male predominance, and identification of several associated genetic loci (Olivé & Endom, 2019; Seifarth & Soldes, 2016).

Regional variations in the prevalence of HPS suggest environmental factors contribute to the development of HPS (Olivé & Endom, 2019). Other environmental factors that are thought to increase the risk for developing HPS include bottle feeding (McAteer, Ledbetter, & Goldin, 2013), maternal smoking (Svenningsson, Svensson, Akre, & Nordenskjöld, 2014), and exposure to macrolide antibiotics (Eberly, Eide, Thompson, & Nylund, 2015).

Diagnosis

Infants with HPS typically develop symptoms between 3 and 6 weeks of age. The predominant symptom is nonbilious forceful ("projectile") emesis that occurs almost immediately after feeding (Olivé & Endom, 2019). If the vomiting has gone on for some time, there may be evidence of brown coloration or blood streaks from vomiting-induced gastritis or esophagitis. The infant often exhibits a robust appetite even after vomiting episodes. The inability to tolerate feedings may result in dehydration, lethargy, and failure to thrive. Abdominal examination may reveal the hypertrophied pylorus as an olive-shaped mass at the lateral edge of the rectus abdominis muscle in the right upper quadrant of the abdomen (Olivé & Endom, 2019). Since adrenal crisis associated with congenital adrenal hyperplasia may also present with significant vomiting, examination for evidence of ambiguous genitalia should also be part of the physical examination (Olivé & Endom, 2019).

Laboratory abnormalities classically reveal hypochloremic, hypokalemic metabolic alkalosis (Olivé & Endom, 2019). The CBC is usually normal in infants with HPS. A mild unconjugated hyperbilirubinemia may also be present (Olivé & Endom, 2019). Abdominal ultrasound has a sensitivity and specificity of greater than 95% when performed by experienced technicians or radiologists (Niedzielski, Kobielski, Sokal, & Krakós, 2011). The diagnostic appearance on ultrasound is a target sign that represents the outer ring of low echo density musculature and the inner ring of high echo density mucosa (Seifarth & Soldes, 2016). Since HPS can evolve over time, a previous "normal" ultrasound should not preclude repeating the study if the infant's symptoms persist or worsen.

If ultrasonography is unavailable or inconclusive, an upper GI contrast study may be obtained. The most common signs on upper GI are an elongated and narrowed pyloric channel ("string" sign), two thin tracks of contrast along the pyloric channel from the compressed pyloric mucosa ("double-track" sign), a tapered point ending the pyloric channel ("beak" sign), and a prepyloric bulge of contrast ("shoulder" sign; Olivé & Endom, 2019).

Management

Pyloromyotomy is the surgical treatment for HPS. Prior to surgery, dehydration and electrolyte abnormalities should be corrected. Multiple boluses with 10 to 20 mL/kg of 0.9% normal saline may be required to correct the hypovolemia. Maintenance fluid then can be started with 5% dextrose in 0.45% to 0.9% saline at 1.5 to 2.0 times the maintenance rate depending on the degree of dehydration (Olivé & Endom, 2019). Once urine output is established, 10 to 20 mEq/L of potassium chloride may be added to the IV fluid mixture (Seifarth & Soldes, 2016). Electrolytes should be monitored every 8 to 12 hours until normalized. Surgery may be delayed for 24 to 48 hours in order to correct dehydration and electrolyte abnormalities (Hackam, Upperman, Grikscheit, Wang & Ford, 2019). Unlike other abdominal surgical conditions associated with

vomiting, continuous suction with a NG tube should be avoided so as not to exacerbate electrolyte abnormalities.

There are no guidelines on the timing and type of feedings to start after surgery. A common protocol used at some centers begins feedings within 4 to 8 hours after surgery. One-half to 1 oz of an electrolyte solution is started and progresses every 2 to 3 hours to 2 oz of breast milk or formula (Seifarth & Soldes, 2016). Most infants can be discharged within 48 hours after surgery (Seifarth & Soldes, 2016).

INTESTINAL ATRESIA

Background

Intestinal atresia (IA) is defined as a congenital defect of a hollow viscus resulting in complete or partial obstruction of the bowel lumen (Wesson, 2018). Duodenal atresias make up approximately 50% of intestinal atresias (Wesson, 2018). The classification scheme for duodenal atresia is summarized in Table 8.10. Duodenal atresia is hypothesized to be caused by a failure of luminal recanalization during weeks 8 to 10 of embryonic development (Schneider & Oldham, 2016). Up to 30% of infants with duodenal atresia may have associated chromosomal anomalies such as trisomy 21 (Best et al., 2012).

Jejunal and ileal atresia each make up 20% of IAs (Best et al., 2012). Unlike duodenal atresia, the pathophysiologic model for jejunal and ileal atresias begins with vascular compromise that leads to intestinal necrosis and subsequent reabsorption of the bowel tissue (Louw, 1959). Examples of causes of vascular compromise may include intussusception, segmental compromise of the mesenteric blood supply, volvulus, internal herniation, and gastroschisis (Wesson, 2018). Less than 5% of patients with jejunal or ileal atresia have associated chromosomal abnormalities (Best et al., 2012).

TABLE 8.10

CLASSIFICATION OF DUODENAL ATRESIA

Type	Description
I	• Intestinal lumen obstructed by a membrane • Membrane obstruction complete or fenestrated
II	• Fibrous band connecting two ends of duodenum
III	• Two blind-ending bowel loops; no mesentery in between • May be associated with biliary anomalies • Least common type

Classification of Jejunal Atresia

Type	Description
I	• Intraluminal web in continuity with muscle layers of proximal and distal segments • Least common type
II	• Fibrous cords connect proximal and distal bowel segments
III	• Significant mesenteric defects • Subtype IIIA—V-shaped mesenteric defect with intestinal discontinuity • Subtype IIIB—mesenteric defect with distal segment receiving entire blood supply in retrograde fashion via ileocolic or right colic artery. "Apple peel" or "Christmas tree" deformity • Associated with significant bowel loss • Most common type
IV	• Multiple atresias within a single length of bowel

Sources: Adapted from: Best, K. E., Tennant, P. W., Addor, M. C., Bianchi, F., Boyd, P., Calzolari, E., . . . Rankin, J. (2012). Epidemiology of small intestinal atresia in Europe: A register-based study. *Archives of Disease in Childhood—Fetal and Neonatal Edition, 97*(5), F353–F358. doi:10.1136/fetalneonatal-2011-300631; Schneider, J. G., & Oldham, K. T. (2016). Atresia and stenosis of the bowel. In R. Wyllie, H. S. Hyams, & M. Kay (Eds.), *Pediatric gastrointestinal and liver disease* (5th ed., pp. 648–653). Philadelphia, PA: Elsevier.; Wesson, D. E. (2018). Intestinal atresia. In J. A. Garcia-Prats & M. B. Heyman (Eds.), *UpToDate.* Retrieved from https://www.uptodate.com/contents/intestinal-atresia

Diagnosis

IA typically presents within the first 72 hours of life. These newborns may have abdominal distension, bilious or nonbilious vomiting, or fail to pass meconium (Wesson, 2018). A supine anteroposterior plain radiograph with either upright, lateral decubitus, or cross-table lateral views should be obtained in neonates and infants with suspected intestinal obstruction. Table 8.11 summarizes the possible findings on plain radiography.

Duodenal Atresia. Less than 50% of IAs are diagnosed prenatally (Haeusler, Berghold, Stoll, Barisic, & Clementi, 2002). Prenatal ultrasound of neonates with duodenal atresia may show polyhydramnios and/or dilation of the stomach and proximal duodenum (Grosfeld & Rescorla, 1993). The vomiting-associated duodenal atresia is typically bilious. Abdominal distension may or may not be present as vomiting may be sufficient to decompress proximal obstructions (Schneider & Oldham, 2016). Abdominal radiograph often reveals simultaneous gastric and duodenal distension (double bubble sign) with a paucity of air in the remainder of the bowel.

Jejunal Atresia. Prenatal ultrasound in neonates with jejunal atresia may show polyhydramnios and dilated loops of bowel (Phelps, Fisher, Partington, & Dykes, 1997). Infants may present with bilious vomiting, abdominal distension, and/or jaundice. Plain radiograph may show moderate to severely dilated bowel

TABLE 8.11

PLAIN RADIOGRAPH FINDINGS OF SELECTED INTESTINAL PATHOLOGIES

Diagnosis	Plain Radiograph Finding
Intestinal perforation	Abnormal accumulation of extraintestinal air Pneumoperitoneum Intraperitoneal calcification—(prenatal intestinal perforation, meconium peritonitis)
Duodenal atresia	Double bubble sign (dilation of stomach and duodenum) Absence or paucity of air in distal bowel Air-fluid level in duodenum
Jejunal or ileal atresia	Dilated loops of small bowel with air-fluid levels
Malrotation	Contrast study findings: Low-lying or displaced duodenojejunal junction and coiling of bowel with partial or complete obstruction

loops and air-fluid levels. A rectal contrast enema may reveal a microcolon in the setting of small bowel atresia.

Contrast Studies. If there is no evidence of perforation on plain radiograph, most infants should undergo an upper GI contrast study to look for malrotation or midgut volvulus. If plain radiographs and upper GI contrast studies do not provide a likely diagnosis, a contrast enema should be considered to further evaluate for IA or other causes of intestinal obstruction (Wesson, 2018).

Evaluation for other associated congenital anomalies should be considered as summarized in Table 8.12 (Kimble, Harding, & Kolbe, 1997).

Management

Definitive treatment for IA is operative. Preoperative therapy includes electrolyte and fluid resuscitation, antibiotics, and upper GI decompression via an orogastric or NG tube. An echocardiogram may be warranted to look for associated cardiac anomalies, particularly in patients with a murmur or trisomy 21.

Postoperatively, GI decompression is continued. PN may be required until oral feedings are started. Once the gastric aspirate appears clear and there is evidence of GI function, feeds can be started and carefully advanced until full enteral feeds are tolerated. Achieving full enteral feeds may take several weeks (Schneider & Oldham, 2016). Patients who require extensive bowel resection may take longer to tolerate enteral feeds or develop short bowel syndrome (SBS) requiring chronic PN therapy.

INTESTINAL MALROTATION

Background

Normal intestinal development in the fetus follows an orchestrated sequence of growth, elongation, and rotation followed by intestinal fixation to the body wall during fetal development (Table 8.13; Sato & Chang, 2016). Malrotation occurs when any step in this process fails to happen, resulting in abnormal intestinal rotation and fixation (Sato & Chang, 2016). The most catastrophic complication of malrotation occurs when the intestine twists along its mesenteric axis, resulting in volvulus, bowel ischemia, necrosis, and loss of bowel. Approximately 30% of infants with malrotation presenting before 1 month of age will develop volvulus (Fonkalsrud, 2003). Fifty percent of infants with malrotation are diagnosed in the first month of life and 90% by 1 year of age (Ford, Senac, Srikanth, & Weitzman, 1992; Nehra & Goldstein, 2011; Sato & Chang, 2016).

Other anomalies associated with intestinal malrotation include congenital diaphragmatic hernia, cardiac anomalies, abdominal wall defects (omphalocele, gastroschisis, prune belly syndrome), IA, EA, biliary atresia, Meckel's diverticulum, ARM, and Cornelia de Lang syndrome (Brandt, 2019).

TABLE 8.12

ADDITIONAL TESTING TO CONSIDER IN PATIENTS WITH INTESTINAL ATRESIA

Test	Consider in Neonates and Infants With. . .
Echocardiogram	Duodenal atresia Down syndrome
Chest radiograph	Infants with any small bowel atresia looking for vertebral anomalies
Renal ultrasound	Duodenal atresia
Cystic fibrosis mutation testing	Small bowel atresia and meconium plugs

Source: Adapted from Kimble, R. M., Harding, J., & Kolbe, A. (1997). Additional congenital anomalies in babies with gut atresia or stenosis: When to investigate, and which investigation. *Pediatric Surgery International, 12*, 565. doi:10.1007/bf01371900

Diagnosis

Since malrotation can quickly evolve into catastrophic volvulus, evaluation and treatment should be pursued emergently. Newborns and infants with malrotation typically present with one or

TABLE 8.13

FETAL EVENTS LEADING TO NORMAL POSITION OF THE INTESTINES

Stage	Event
I	• Fifth week of gestation • Herniation of primary intestinal midgut loop into umbilical cord base • Omphalomesenteric duct located at apex of midgut loop rotates 180° counterclockwise so that proximal prearterial half of loop passes posterior to SMA. • Prearterial segment gives rise to proximal duodenum (right of midline). • Distal prearterial segment that passes posterior and to the left of SMA becomes third and fourth portions of duodenum. • Distal duodenum normally fixed to left of aorta at ligament of Treitz after 270° counterclockwise rotation from original position. • Jejunoileal segment elongates to form remainder of small bowel. • Postarterial segment gives rise to cecum and right colon which undergoes a 270° counterclockwise rotation to move from the initial position on the left to the right of SMA before attaching to posterior wall of right iliac fossa.
II	• 10th–12th week gestation • Duodenojejunal junction has passed posterior to SMA and midgut rotated 180° counterclockwise • Small intestine initially remains to right of midline; cecum and ascending colon still anterior to SMA on return of the intestine to the abdominal cavity
III	• 12th week of gestation • Normal points of fixation: cecum in right iliac fossa, duodenojejunal junction at ligament of Treitz • Fixation of intestines to posterior body wall with a broad base extending from ligament of Treitz to cecum • Fixation prevents torsion of intestinal mesentery around its vascular supply

SMA, superior mesenteric artery.

Source: Adapted from Sato, T. T., & Chang, H. L. (2016). Abnormal rotation and fixation of the intestine. In R. Wyllie, H. S. Hyams, & M. Kay (Eds.), *Pediatric gastrointestinal and liver disease* (5th ed., pp. 640–647). Philadelphia, PA: Elsevier.

more of the following symptoms and signs: bilious or nonbilious vomiting, abnormal abdominal examination (distension, tenderness), and hemodynamic instability. Irritability, lethargy, feeding intolerance, reduced oral intake, and/or poor growth are nonspecific findings that may also suggest malrotation.

Emergency Alert: Late findings in babies with intestinal malrotation or volvulus include persistent bilious emesis associated with hemodynamic instability (tachycardia, hypotension, tachypnea), persistent abdominal distension, peritoneal signs, and poor vascular perfusion. Evaluation may reveal occult blood positive stools, metabolic acidosis, elevated serum lactate, and coagulopathy (Brandt, 2019; Nehra & Goldstein, 2011; Sato & Chang, 2016).

In a patient with suspected volvulus who is hemodynamically unstable, imaging should not delay surgical exploration (Brandt, 2019). Radiographic studies can proceed in hemodynamically stable patients. Initial plain abdominal radiography may reveal gastric or proximal bowel distension with a paucity of distal bowel air on plain abdominal radiographs. Upright anteroposterior or cross-table lateral views to look for pneumoperitoneum suggestive of intestinal perforation should also be obtained.

If there is no evidence of perforation on plain radiographs, an upper GI contrast study should be performed to confirm malrotation (Applegate, 2009). Malrotation may appear as a corkscrew or coiled spiral pattern with contrast imaging. The position of the duodenojejunal junction or ligament of Treitz on the right side of the abdomen also suggests malrotation (Applegate, 2009). Upper GI contrast studies have a sensitivity of over 90% for detecting malrotation (Sizemore, Rabbani, Ladd, & Applegate, 2008). For infants who undergo rectal contrast enema, the cecum may be positioned in the midline or to the left of the vertebra. However, it should be noted that in 20% of cases of malrotation, the cecum may appear in its normal anatomic location in the right lower quadrant (Applegate, 2009).

Ultrasound is a modality that is gaining increasing popularity. Normally, the superior mesenteric vein is to the right of the superior mesenteric artery (SMA). In the presence of malrotation, the superior mesenteric vein may be found ventral or to the left of the SMA (Sato & Chang, 2016; Weinberger, Winters, Liddell, Rosenbaum, & Krauter, 1992). It should be noted that a normal ultrasound does not eliminate the possibility of malrotation (Ashley, Allen, & Teele, 2001; Orzech, Navarro, & Langer, 2006).

Management

Prompt consultation with pediatric surgeons is paramount in all cases of suspected malrotation or volvulus. Preoperative management includes NG tube decompression and circulatory and electrolyte resuscitation. Broad-spectrum antibiotics should be considered since signs and symptoms of malrotation/volvulus can overlap with sepsis, or there may be concomitant systemic infection. Acid suppression with a H_2A blocker should be considered since vomiting or the presence of a NG tube may increase the risk for developing gastritis or esophagitis.

A general operative approach is shown in Box 8.1.

Recovery of GI function may be delayed postoperatively, particularly in the presence of volvulus; prolonged nasogastric decompression and PN may be required (Feitz & Vos, 1997; Sato & Chang, 2016). Some infants and children may have persistent postoperative vomiting or feeding intolerance with intestinal motility patterns that mimic neuropathic intestinal pseudo-obstruction (Devane et al., 1992). Prokinetic agents such as metoclopramide or erythromycin can be considered along with continued acid suppression therapy in postoperative infants with persistent symptoms of dysmotility. Neonates who require extensive bowel resection due to a delay in diagnosis may develop SBS necessitating chronic PN therapy.

Box 8.1

GENERAL OPERATIVE STRATEGY FOR MALROTATION AND VOLVULUS

- Delivery of the entire midgut and inspection of vascular mesentery
- Reduction of volvulus and evaluation of intestinal viability
- Division of Ladd's bands
- Broadening the base of mesenteric vascular pedicle
- Appendectomy
- Return of GI tract with small intestine in the right abdomen and the large intestine in the left abdomen.

Source: Data from Abdullah, F., & Karim, O. (2018). *BMJ Best Practice: Intestinal malrotation*. London, England: BMJ Publishing Group.

ABDOMINAL WALL DEFECTS

Background

The prevalence of omphalocele and gastroschisis is approximately 3 to 4 per 10,000 live births (Friedman, Ananth, Siddiq, D'Alton, & Wright, 2016).

An omphalocele is a midline abdominal wall defect of variable size that is typically covered by a membrane of amnion and peritoneum that contains abdominal contents. The defect is at the base of the umbilical cord with the umbilical vessels inserting into the apex of the omphalocele sac. Sac contents may include stomach, small bowel loops, colon, and liver. The bowel may appear matted and edematous as a result of chronically being exposed to amniotic fluid. Larger omphaloceles may also contain the bladder, gonads, and spleen. The pathogenesis of omphaloceles begins during week 3 to 4 of fetal development when the embryo lengthens and folds onto itself to enclose various body cavities. Two lateral folds normally form and meet anteriorly in the midline at the umbilicus. Failure of the folds to meet in the midline results in an omphalocele (Stephenson, Lockwood, & MacKenzie, 2018).

Gastroschisis is an abdominal wall defect that is usually 5 cm or less and located to the right of the umbilical cord. The herniated abdominal contents usually include only the small bowel. The pathogenesis of gastroschisis is less clear. Several hypotheses have been proposed including failure of differentiation of the embryonic mesenchyme, rupture of the amniotic membrane at the base of the umbilical cord at the area of the right umbilical vein, and vascular compromise (deVries, 1980).

Diagnosis

The diagnosis of gastroschisis and omphalocele is usually made by prenatal ultrasound. Omphalocele can be differentiated from gastroschisis by the presence of a sac and a liver within the defect in most cases (Stephenson et al., 2018). Gastroschisis can be identified by free-floating loops of bowel within the amniotic fluid. Ultrasound may also detect associated anomalies such as IA and cardiac defects (Hughes, Nyberg, Mack, & Pretorius, 1989; Walther & Nathan, 2016; see Table 8.14). Both omphalocele and gastroschisis can be associated with elevated maternal serum alpha fetoprotein (Saller, Canick, Palomaki, Knight, & Haddow, 1994).

Omphalocele can be associated with chromosomal abnormalities such as trisomy 18 or 13, Turner syndrome, and triploidy. Structural anomalies may include other GI anomalies, cardiac

TABLE 8.14

COMPARISON OF GASTROSCHISIS AND OMPHALOCELE

	Gastroschisis	Omphalocele
Incidence	1 in 2,000 live births	1 in 5,000 live births
Defect location	Right periumbilical	Umbilical ring/central
Covering sac	Absent	Present (amnion and peritoneum)
Description	Free intestinal loops	Firm mass including bowel, liver, etc.
Umbilical cord	Normal insertion	Inserts into sac
Necrotizing enterocolitis	Common	Uncommon
Associated anomalies	• Gastrointestinal • Intestinal atresia • Malrotation • Cryptorchidism • Stenosis • Perforation • Volvulus	• Trisomy syndromes • Cardiac defects • Beckwith–Weidemann syndrome • Bladder exstrophy

Source: Adapted from Chabra, S., & Gleason, C. A. (2005). Gastroschisis. *NeoReviews, 6*(11), e493–e499. doi:10.1542/neo.6-11-e493; Walther, A. E, & Nathan, J. D. (2016). Newborn abdominal wall defects. In R. Wyllie, H. S. Hyams, & M. Kay (Eds.), *Pediatric gastrointestinal and liver disease* (5th ed., pp. 654–665). Philadelphia, PA: Elsevier.

defects, genitourinary anomalies, orofacial clefts, neural tube defects, and diaphragmatic defects (Stephenson et al., 2018). Other syndromes associated with omphalocele include Pentalogy of Cantrell, amniotic band sequence, schisis association, OEIS syndrome (omphalocele, exstrophy of the bladder, imperforate anus, spinal defects), Shprintzen syndrome, Carpenter syndrome, Goltz syndrome, Marshall–Smith syndrome, CHARGE syndrome, and Beckwith–Wiedemann syndrome (Stephenson et al., 2018).

Management

Presurgical management of infants with gastroschisis or omphalocele presents added challenges compared to infants with other surgical conditions. Infants with respiratory distress may require supplemental oxygen or ventilator support. Intravenous lines should preferentially be placed in the upper extremities due to possible inferior vena cava (IVC) compression during bowel reduction (Walther & Nathan, 2016). A nasogastric or orogastric tube should be placed to decompress the stomach and help minimize small bowel distension.

The omphalocele sac should be wrapped with saline-soaked gauze and an impervious dressing to reduce fluid losses and hypothermia. In neonates who have gastroschisis with eviscerated bowel, or a ruptured omphalocele, the bowel should be wrapped in saline-soaked gauze and placed in a central position; the infant should be placed on the right side to prevent vascular compromise from mesenteric kinking. The bowel is then wrapped in an impervious dressing, such as a plastic wrap (BMJ Best Practice, 2017; Walther & Nathan, 2016).

If the gastroschisis defect is small and there is evidence of vascular compromise, the defect should be enlarged to increase flood flow (Walther & Nathan, 2016). Infants should be placed in a warm environment to maintain core body temperature. Due to ongoing fluid losses, infants may require fluid volumes greater than maintenance amounts. Electrolytes should be followed closely and corrected as needed. Repositioning the baby may be needed if there are signs of vascular compromise to the bowel such as hypotension, tachycardia, or a dusky bowel appearance.

Surgical options for gastroschisis include primary reduction and fascial closure, silo placement with serial reduction, and delayed fascial closure, or primary or delayed reduction without fascial closure (BMJ Best Practice, 2017; Walther & Nathan, 2016). The main goal in managing omphalocele is the gradual reduction of the viscera into the abdominal cavity, followed by closure of the fascia and skin. Central venous access should be secured in anticipation of lengthy postoperative PN needs associated with intestinal dysmotility that is frequently encountered.

For neonates with omphalocele, the priority for abdominal wall repair is preservation of blood flow to the intestines and eviscerated organs (Stephenson, Lockwood, & MacKenzie, 2019). Small defects (2–3 cm) can usually be closed in the first 24 to 72 hours of life (Stephenson et al., 2019). Larger and more complex defects may require initial silo placement followed by gradual reduction and definitive closure (Pacilli, Spitz, Kiely, Curry, & Pierro, 2005). Depending on the size of the abdominal wall defect, it may take 3 to 7 days before sufficient reduction is achieved to allow closure of the fascia and skin. Serial Doppler ultrasound may be used to ensure sufficient blood flow to the organs during the omphalocele reduction process.

During the postoperative period, infants are at risk of developing abdominal compartment syndrome after fascial closure. Repeated physical examination, ventilator settings, intra-abdominal pressure measurements, heart rate, blood pressure, and urine output may provide clues indicating increased abdominal pressure (Stephenson et al., 2018). NG or orogastric decompression should continue until there is clinical evidence of bowel function and the abdominal examination is reassuring. PN should continue until a sufficient volume of enteral calories is reached. There is no clear consensus as to the optimal time for starting enteral feeds. Tolerance of full enteral feedings may take time due to the intestinal dysmotility commonly associated with gastroschisis. However, introducing even the smallest amounts of enteral feedings may help lower the risk of developing cholestasis as a result of delayed enteral feedings and PN. Oral stimulation should be provided as much as possible even during the slow process of advancing feeds to minimize the risk of developing feeding problems from the loss of the suck–swallow reflex (Walther & Nathan, 2016).

NECROTIZING ENTEROCOLITIS

Background

NEC is the most common GI emergency in neonates and carries a high rate of long-term complications (Gregory, DeForge, Natale, Phillips, & Van Marter, 2011). NEC occurs in 1 to 3 per 1,000 live births and increases with decreasing gestational age (Llanos et al., 2002; Thompson & Bizzarro, 2008). While NEC can occur at any age, approximately 90% occur in preterm infants who have been fed enterally (Kim, 2019a; Yee et al., 2012). Characteristics inherent to premature infants that most likely contribute to their increased risk for developing NEC are circulatory instability, permeable GI mucosal barrier that is prone to bacterial translocation, undeveloped local host defense mechanisms, and immature bowel motility and function (Kim, 2019b).

NEC can be localized in the case of segmental mucosal necrosis or extensive in the case of transmural necrosis of the small and large bowels. While the pathogenesis of NEC is not well defined, characteristic features most likely include ischemic injury leading to necrosis of the intestinal mucosa, unregulated mucosal inflammation, abnormal bacterial colonization particularly by gas-forming organisms, and dissection of gas into the muscularis layer of the intestines and portal venous system (Kim, 2018; Neu & Walker, 2011). The convergence of these pathogenic mechanisms culminates in multiorgan system failure (Iben & Rodriguez, 2016).

Diagnosis

Clinical evidence of NEC can be nonspecific such as increased gastric residual with feeds, poor feeding, apnea, lethargy, temperature instability, vomiting, change in stool character, occult blood positive stools, abdominal distension or tenderness, discoloration of abdominal skin, and/or bilious output from enteral feeding tubes (Kim, 2019a). Respiratory failure and signs of septic shock may also be present. Bacteremia is also common with NEC (Kim, 2019a). Laboratory findings may include leukocytosis, neutropenia, disseminated intravascular coagulation (increased prothrombin time, decreased fibrinogen, increased fibrin split products), acute anemia, thrombocytopenia or thrombocytosis, elevated C-reactive protein, hyperglycemia, electrolyte abnormalities (hyponatremia common), and acidosis (metabolic/respiratory; Kim, 2019a). Contrast enemas are contraindicated in suspected NEC due to the risk of perforation.

Successful management of NEC begins with early diagnosis that stems from being vigilant to clinical changes (Table 8.15). When NEC is suspected, screening assessment can include plain abdominal radiography, stool for occult blood and calprotectin, sepsis evaluation, CBC, coagulation studies, and serum chemistries (electrolytes, CO_2, BUN, Cr, glucose, lactate). Plain abdominal radiographs should include cross-table lateral and/or left lateral decubitus views to help detect pneumoperitoneum. Other abdominal radiographic signs can range from nonspecific findings such as a gasless abdomen, ascites, and dilated loops of bowel to ominous signs including pneumatosis intestinalis, portal venous air, or sentinel loops. Pneumatosis intestinalis is the result of gas dissecting into the bowel wall. Sentinel loops are bowel loops that remain in a fixed position on serial radiographs and may be evidence for necrotic bowel and/or perforation (Kim, 2019a).

Abdominal ultrasonography is likely to play an increasingly important role in the evaluation and diagnosis of NEC (Garbi-Goutel et al., 2014; Silva et al., 2007). A central echogenic focus with a hypoechoic rim may suggest necrotic bowel. Ultrasonography may also identify air in the liver parenchyma and portal venous system, fluid collections, and/or changes in bowel wall thickness and echogenicity associated with NEC. Doppler ultrasound can also detect abnormal bowel wall perfusion (Garbi-Goutel et al., 2014; Kim, 2019a; Silva et al., 2007).

TABLE 8.15

MODIFIED BELL STAGING CRITERIA FOR NEC

Stage	Classification	Systemic Signs	Intestinal Signs	Radiographic Signs
IA	Suspected NEC	Temperature instability, apnea, bradycardia, lethargy	Increased gastric residuals, mild abdominal distension, vomiting, guaiac-positive stool	Normal or dilated bowel loops, mild ileus
IB	Suspected NEC	Same as IA	Bright red blood from rectum	Same as above
IIA	Proven NEC—mildly ill	Same as above	Same as above, plus absent bowel sounds, with or without abdominal tenderness	Intestinal dilation, ileus, pneumatosis intestinalis
IIB	Proven NEC—moderately ill	Same as above plus: mild metabolic acidosis, mild thrombocytopenia	Same as above, plus absent bowel sounds, abdominal tenderness, with or without abdominal cellulitis or right lower quadrant mass	Same as IIA, plus portal venous gas, with or without ascites
IIIA	Advanced NEC—severely ill, bowel intact	Same as IIB, plus hypotension, bradycardia, severe apnea, combined respiratory and metabolic acidosis, disseminated intravascular coagulation, and neutropenia	Same as above, plus signs of generalized peritonitis, marked tenderness, and distention of abdomen	Same as IIB, plus definite ascites
IIIB	Advanced NEC—severely ill, bowel perforated	Same as IIIA	Same as IIIA	Same as IIB, plus pneumoperitoneum

NEC, necrotizing enterocolitis.

Source: With permission from Gregory, K. E., DeForge, C. E., Natale, K., Phillips, M., & Van Marter, L. J. (2011). Necrotizing enterocolitis in the premature infant: Neonatal nursing assessment, disease pathogenesis, and clinical presentation. *Advances in Neonatal Care, 11*(3), 155–164. doi:10.1097/ANC.0b013e31821baaf4

Management

Management of NEC begins with bowel rest (nil per os—NPO), prompt initiation of broad-spectrum antibiotics, and abdominal decompression. Decompression via a NG tube set to low suction is continued until there is clinical improvement, and the abdominal distension and any pneumatosis that is present resolves. Since the period of NPO can range from 10 to 14 days, PN should provide complete nutritional requirements. Inotropic support, large volume fluid resuscitation, and ventilator support may be needed in some infants who become critically ill. Close monitoring and correction of electrolyte and metabolic abnormalities also will be required in many infants with NEC (Iben & Rodriguez, 2016; Kim, 2019a).

Since up to 30% of infants with NEC will have concomitant bacteremia (Ballance, Dahms, Shenker, & Kliegman, 1990; Holman, Stoll, Clarke, & Glass, 1997; Hunter, Upperman, Ford, & Camerini, 2008; Kim, 2018; Neu & Weiss, 1999), blood cultures should be obtained prior to antibiotic therapy. There are several broad-spectrum antibiotic combination options, but any regimen should include coverage of gram-negative and anaerobic organisms (Kim, 2018). **Quality and Safety: Antifungal therapy should additionally be considered if there is suspicion for intestinal perforation or if the neonate is critically ill.** The length of antimicrobial therapy is typically 10 to 14 days. Enteral feedings can be restarted after 10 to 14 days of NPO as the clinical picture improves. Enteral feeds are advanced slowly so as to reach full feeds over 7 to 10 days (Iben & Rodriguez, 2016). Given the potential for significant bowel injury with NEC, normal GI function including digestion, absorption, and motility may be slow to return.

A CBC with differential, electrolytes, creatinine, BUN, and acid-base tests should be obtained every 12 to 24 hours in the acute stages of managing NEC. The frequency of monitoring serum lactate, liver enzymes, and coagulation studies should be guided by the initial results of these studies. **Emergency Alert: Worsening or persistent low platelet count, metabolic acidosis, or increasing serum glucose are associated with worsening or persisting NEC (Kim, 2019b).** Plain radiographs taken every 6 to 12 hours in the initial acute phase of NEC is likely a prudent strategy. Radiographs should also be obtained as needed for any clinical change or deterioration.

The timing of surgical intervention, if necessary, requires clinical judgment and evaluation of the overall clinical condition in close consultation with pediatric surgeons. Indications for surgical intervention may include lack of clinical improvement with medical management, worsening clinical picture, free intra-abdominal air, or suspected bowel necrosis. **Emergency Alert: Worsening laboratory values (metabolic acidosis, thrombocytopenia, coagulopathy), inability to ventilate, persistent or worsening skin discoloration, protracted or refractory hypotension, persistent or worsening thrombocytopenia, or fixed bowel loops on plain radiography are signs that should trigger consideration of surgical management.** Surgical options include bedside placement of Penrose drain(s) with or without irrigation, or open laparotomy. The main aim of open laparotomy is removal of necrotic bowel, irrigation of contaminated abdominal cavity, and proximal diversion with the goal of preserving viable bowel (Iben & Rodriguez, 2016; Kim, 2018).

INTESTINAL FAILURE AND SHORT BOWEL SYNDROME

Background

At 27 weeks' gestation, the length of the average small bowel is 100 cm and increases to 200 cm by 40 weeks of gestation (Struijs, Diamond, de Silva, & Wales, 2009). By 3 years of age, the mean intestinal small bowel length is 350 cm. SBS is most commonly used to describe patients whose native bowel length or bowel function is insufficient to digest and absorb the appropriate nutrients and liquids for normal growth and hydration. However, the term SBS may be misleading in that the name implies a deficiency in the length of bowel, which may or may not be accurate depending on the underlying etiology. For example, infants who have a normal bowel length but depend exclusively on PN secondary to congenital villus pathology are often referred to as "SBS." A second and perhaps more accurately encompassing term is *intestinal failure* (IF).

IF is defined as the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, such that intravenous supplementation is required to maintain health and/or growth (Pironi et al., 2015). The reduction of gut absorptive function that does not require intravenous supplementation to maintain health and/or growth can be considered as "intestinal insufficiency" (Pironi et al., 2015). Thus, IF is a broader umbrella term that encompasses SBS.

The ultimate goal for all infants with SBS who initially require PN is transition to full oral or enteral feedings. While there are no perfect predictors of weaning from PN, it is generally thought that longer bowel length, the presence of an intact ileum and ileocecal valve (ICV), the presence of a colon, and continuity of the GI tract represent favorable prognostic factors for weaning from PN (Andorsky et al., 2001; Goulet et al., 2005; Infantino et al., 2013; Quirós-Tejeira et al., 2004; Sondheimer, Cadnapaphornchai, Sontag, & Zerbe, 1998).

Intestinal adaptation refers to the physiologic and anatomic changes that the intestine undergoes over time that enables an increase in its digestive and absorptive functions (Kaufman, 2016). The large surface area, along with its high concentration of digestive enzymes and density of transport proteins, makes the jejunum the primary site for digestion and absorption of most macronutrients, micronutrients, and fluids. Thus, a functional or anatomic loss of the jejunum results in a corresponding loss of nutrient absorption.

The ileum also plays an important role in the absorption of fluids entering from the jejunum. In addition, it is the primary site for vitamin B_{12} absorption and bile acid reabsorption. Malabsorption of vitamin B_{12} results in macrocytic anemia, while malabsorption of bile acids causes fat and fat-soluble vitamin malabsorption. The ICV serves at least two key physiologic functions that likely contribute to intestinal adaptation. First, the ICV serves as a barrier that blocks the translocation of colonic bacteria into the small intestine where they can flourish and promote small intestine bacterial overgrowth (SIBO). SIBO is thought to contribute to further malabsorption of certain nutrients such as vitamin B_{12} and deconjugation of bile acids that contributes to fat malabsorption and diarrhea (DiBaise, Young, & Vanderhoof, 2006). The ICV is also essential in its role as a physiologic brake, slowing the transit from intestine to colon, and allowing more time for the intestine to carry out its digestive and absorptive functions. Indeed, the presence of an ICV is believed to improve the chances of weaning from PN (Goulet et al., 2005; Quirós-Tejeira et al., 2004).

The causes of IF can further be classified as short bowel syndrome, congenital diseases of enterocyte development, and severe motility disorders (D'Antiga & Goulet, 2013; Goulet & Ruemmele, 2006). In children, the most common cause of IF is SBS. Common causes of SBS in infants include NEC, midgut volvulus, gastroschisis, and IA (D'Antiga & Goulet, 2013; Goulet & Ruemmele, 2006).

Diagnosis

The diagnosis of neonates with SBS is usually straightforward. These patients typically have been diagnosed with NEC,

gastroschisis, omphalocele, intestinal volvulus, or IA, most often associated with surgical bowel resection. Symptoms of feeding intolerance such as massive diarrhea, abdominal distension, and vomiting are also common in patients with SBS.

Other causes of IF in the neonatal period such as congenital villus abnormalities and idiopathic pseudo-obstruction syndrome are less common. However, these causes may exhibit similar symptomatology of feeding intolerance and failure to grow in the neonatal period. Likewise, these babies will also require PN to survive.

In neonates who do require surgical intervention, it is helpful to note the quality, quantity, and location of remaining small bowel and colon on operative reports. A precise understanding of the remaining anatomy can guide management decisions as well as facilitate discussions regarding prognosis with family members.

Management

The mainstay of management of infants with SBS is PN. In order to provide an adequate amount of PN, a central venous catheter should be placed. The quantity of PN should be sufficient to support normal growth, normalization of electrolytes, and maintenance of euvolemia. Initially, it is common for infants with SBS to have excess fluid and electrolyte losses that will need to be accounted for in developing the PN recipe. PN is typically delivered over 24 hours initially. Once a maintenance PN program achieves appropriate growth, stable electrolytes, and euvolemia, the PN nutrition cycle can be compressed to 16 to 18 hours in most infants.

While PN may provide the majority of calories for infants with SBS, it is critical to offer and encourage oral or enteral feedings as much as tolerated. There is no standardized approach to enteral or oral feedings. Stamm and Duggan (2018) have proposed a strategy to feed infants with SBS. Breast milk is preferred when available. In the United States, if breast milk is not available many centers favor a protein hydrolysate or an amino acid–based formula. Hydrolysate and amino acid–based formulas have a theoretical advantage since they eliminate the need for most physiologic digestive processes that may be impaired in infants with SBS. In addition, these formulas may be less likely to trigger an immunologic response that infants with SBS may be at increased risk for developing.

Feedings are usually started at 10% to 20% of goal. After feedings are started, advancement can be considered if stool output is less than 10 stools/day (or <10 g/kg/day) or ostomy output is less than 2 mL/kg/hour, perianal skin irritation is manageable, and urine output is greater than 1 mL/kg/hour. The same authors recommend advancing feedings by 10 to 20 mL/kg/day to a maximum goal of 150 to 200 mL/kg/day. If stool output is 10 to 12 stools/day (or 10 to 20 g/kg/day) or ostomy output is 2 to 3 mL/kg/hour, and there is minimal or mild perineal erythema, then feeds can continue at the same rate without advancement. Intolerance to feedings is suggested by increased abdominal distension, greater than 12 stools/day or greater than 20 g/kg/day or ostomy output greater than 3 mL/kg/hour, moderate or severe perineal breakdown, or urine output less than 1 mL/kg/hour. Any of these signs of feeding intolerance should trigger reduction in the rate of feedings or holding the feeds altogether. When feeds are restarted after being held, restart can commence at 50% to 75% of the previous rate (Stamm & Duggan, 2018). Infants who do not have NG or gastric tube feedings should be offered oral feedings as tolerated.

In general, diarrhea or increased stool output related to oral or enteral intake can be tolerated as long as electrolytes and hydration can be maintained, and the irritant effects of the diarrhea on perianal skin is manageable. Vomiting or spitting up can be managed using a combination of acid suppression and/or prokinetic therapy. As long as oral or enteral feeding does not result in complications such as respiratory symptoms or excess irritability, feedings may continue. Even the smallest amounts of oral or enteral feedings are important. First, enteral feeding is thought to be protective against intestinal failure associated liver disease (IFALD), as oral intake and the passage of nutrient through the GI tract likely help stimulate physiologic hormones that promote hepatic bile flow. Second, infants who do not learn to suckle during infancy are more likely to develop long-term oral aversion, even once intestinal adaptation has occurred and PN is no longer needed. Trophic feedings may also help maintain intestinal mucosal integrity, lowering the risk of bacterial translocation and subsequent bacteremia.

Two complications common in infants requiring PN are IFALD and central catheter-related bloodstream infection (CRBSI). IFALD is suspected when bilirubin levels and/or liver enzymes (alanine aminotransferase, gamma glutamyl transferase, alkaline phosphatase) are persistently high in infants receiving chronic PN. The pathophysiology of IFALD is not well understood, but the cause is likely to be multifactorial. Three likely contributing factors include the toxic effects of PN on the liver, the lack of physiologic stimulation of bile flow associated with regular oral feedings, and the toxic effects of repeated episodes of CRBSI and its associated antimicrobial treatment.

Over the last 10 years, particular interest has been paid to the role of the lipid component of PN in contributing to IFALD. The standard lipid emulsion used in the United States is soy based and contains predominantly omega-6 fatty acids, which is the precursor to a host of pro-inflammatory cytokines that can contribute to IFALD (Nandivada et al., 2013). Alternative lipid emulsions such as fish oil–based products contain a higher proportion of omega-3 fatty acids that are believed to have anti-inflammatory effects. Omegaven® is a fish oil–based lipid emulsion that has been shown to mitigate the effects of IFALD in some infants (Gura et al., 2008; Nandivada et al., 2013). However, Omegaven® is currently available only under investigational study protocols. Smoflipid® is a mixture of soy oil, medium chain triglycerides, olive oil, and fish oil that contains a higher proportion of omega-3 fatty acid and has been recently approved by the United States Food and Drug Administration. However, data on its effectiveness in preventing or treating IFALD is limited (Belza et al., 2017).

Independent of the effects of bacteremia and antimicrobial treatment on the liver, CRBSI represents a leading cause of mortality and morbidity in infants with SBS (Chan & Wu, 2014). The ideal management of CRBSI involves treatment with antibiotic and removal of the central line in cases of severe sepsis or persistent bacteremia (Mermel et al., 2009). Unfortunately, infants only have approximately four (two subclavian and two internal jugular) standard sites for central venous access (Kaufman et al., 2001). Once a central line is removed, the vessel is at risk for scarring, rendering it unsuitable for subsequent access.

Thus, recurrent CRBSI may ultimately lead to loss of vascular access for PN. For patients whose vascular access is exhausted, intestinal transplantation is an option (Kaufman et al., 2001). However, the survival rate of long-term PN remains more favorable than intestinal transplantation. Therefore, management strategies aimed at preventing CRBSI are essential. There are no standard guidelines for the care and management of central lines in pediatric PN patients. At Loma Linda University Children's pediatric intestinal care and home parenteral nutrition program, when a central line is accessed or when a central line site dressing is changed, the site or catheter is cleansed with three alcohol and three chlorhexidine pads or swabs. Each pad or swab is applied for approximately 30 seconds. Care providers are asked to wear a mask and to perform vigorous handwashing for 30 seconds prior to accessing the line site or catheter.

SIBO is not an uncommon problem in babies with SBS. Symptoms of SIBO include abdominal distension, nausea and vomiting,

and increased stool output. Usually SIBO in infants is diagnosed based on clinical symptoms. Therapeutic options may include but are not limited to one of the following agents: metronidazole, trimethoprim-sulfamethoxazole, amoxicillin, or amoxicillin clavulanic acid.

Most infants with SBS have an increase in the production of gastric acid within the first 3 to 6 months after surgery. The increased risk for dyspepsia related to this hypersecretory state and a paucity of oral or enteral feedings can be mitigated by therapy with a H_2A such as ranitidine or famotidine. The agents can be administered enterally, orally, or be added to the PN mixture.

INTUSSUSCEPTION

Background

Intussusception is a common cause of intestinal obstruction that occurs when one segment of the intestine invaginates into an adjacent segment. Intussusception can involve any segment of small or large intestine, but ileocolic intussusception is most common. In most cases, a more proximal bowel segment invaginates into an adjacent distal segment. The majority of cases are idiopathic without an identifiable lead point, which is the part of the bowel or mesentery that prevents reduction of the involved bowel segment after it has telescoped. The proximal segment is referred to as the intussusceptum and the distal segment into which it telescopes is the intussuscipiens. Ileocolic intussusception accounts for approximately 90% of cases (Mandeville et al., 2012). Ileoileocolic, jejunojejunal, jejunoileal, and colocolic intussusceptions are also possible.

The telescoping of one segment of the intestine into an adjacent part is observed periodically during GI endoscopy. These telescoping episodes are a part of normal peristalsis, and typically self-reduce, returning bowel segments to their native states. The majority of these episodes are transient and unlikely to cause any clinical symptoms. Intussusception results when the mesentery of the intussusceptum bowel becomes "stuck" during one of these telescoping events. The consequences of intussusception are twofold: (1) partial or complete small bowel obstruction, and (2) progressive vascular compromise if untreated.

The majority of intussusception is idiopathic. However, in a subset of patients intussusception may be associated with viral or bacterial infections (Arbizu, Aljomah, Kozielski, Baker, & Baker, 2014; Bhisitkul, Todd, & Listernick, 1992; Nylund, Denson, & Noel, 2010). It has been proposed that infections cause hypertrophy of lymphatic tissues, which can serve as a lead point that traps bowel segments in the telescoped position, resulting in intussusception (Vo & Sato, 2019). The greater density of lymph tissue in the terminal ileum helps explain why the majority of intussusception involves the ileum.

Up to 25% of patients with intussusception have an underlying disorder (Vo & Sato, 2019). Some of these underlying disorders can include Meckel's diverticulum (St-Vil, Brandt, Panic, Bensoussan, & Blanchard, 1991), polyps (Hwang, Chu, Chen, & Chen, 2001), small bowel lymphoma (Abbasoğlu et al., 2003), vascular malformations (Morgan, Mylankal, el Barghouti, & Dixon, 2000), and vasculitis (Choong & Beasley, 1998).

Diagnosis

Intussusception presents between 6 and 36 months of age with over 50% presenting during infancy (Mandeville et al., 2012). Infants and toddlers with intussusception typically experience a sudden onset of colic and progressive abdominal pain that is episodic (Ross, 2010). During episodes, the infant or toddler may cry inconsolably and draw its legs up toward the abdomen. A period of lethargy may follow the episodes of pain, which may become more frequent over time. Vomiting is commonly associated with the pain episodes and may begin as nonbilious vomiting that progresses to bilious vomiting as the intussusception becomes fixed. Fever is not a typical feature of intussusception.

Between the episodes of pain, the infant or toddler can appear completely normal, which can make the diagnosis difficult to make in the early stages. The classic triad of intussusception including colicky abdominal pain, vomiting, and red "currant jelly" stools may not be evident until the later stages of the disease. The currant jelly stools are caused by a mixture of intestinal mucus and blood resulting from mucosal sloughing due to vascular compromise (Manning & Little, 2016). A sausage-shaped mass may be palpable on physical examination, but this finding is variable (Ross, 2010).

Abdominal ultrasound is noninvasive, safe, and often the test of choice to screen for intussusception. The sensitivity of the technique is nearly 100% when performed by experienced ultrasonographers and interpreted by radiologists familiar with diagnosing intussusception (Mandeville et al., 2012). The classic finding of intussusception on ultrasound is a "target sign," which forms when layers of intestines are trapped within intestine (Manning & Little, 2016).

Rectal enemas using air or contrast can be employed for diagnostic or therapeutic purposes in infants and children with suspected intussusception. A plain abdominal radiograph is performed prior to enemas to confirm the absence of pneumoperitoneum that may suggest intestinal perforation. The hydrostatic or pneumatic pressure from the enema relieves the intussusception in 70% to 80% of cases (Manning & Little, 2016). Contraindications to rectal enemas include evidence of intestinal perforation or peritonitis.

Management

Depending on the infant or toddler's clinical status, there are nonoperative and operative management options. Patients who are hemodynamically stable and have no concerns for intestinal perforation or peritonitis are candidates for nonoperative management. Even when the nonoperative approach is tried first, the surgical team should be consulted in case operative management is required emergently.

Intravenous resuscitation and broad-spectrum antibiotics should be initiated prior to nonoperative or operative management. A NG tube for decompression can be considered if there is gastric or abdominal distension or persistent vomiting. Nonoperative management typically involves a rectal enema using air and/or hydrostatic pressure. Ideally, the pressure should separate the proximal and distal segments of the intussusception. Nonoperative management is successful in 60% to 90% of cases (Heurn, Pakarinen, & Wester, 2014)

Surgical management is indicated in patients who are clinically unstable, have evidence of intestinal perforation or peritonitis, or in whom nonoperative reduction has been unsuccessful. Surgical options include an open or laparoscopic approach. The goal of either approach is to first attempt to manually reduce the involved intestinal segments. If manual reduction is unsuccessful or if a lead point is identified, then resection with primary anastomosis is performed (Heurn et al., 2014).

CONGENITAL AGANGLIONIC MEGACOLON (HIRSCHSPRUNG'S DISEASE)

Background

Normal intestinal motility depends on the coordinated contraction and relaxation of the longitudinal and circular muscle layers throughout the GI tract. Control of motility relies on the function of ganglia that innervate the muscle layers. HD or congenital aganglionic megacolon is a congenital motor disorder of the colon

caused by failure of neural crest cells to migrate completely to the muscular layers during fetal intestinal development (Heuckeroth, 2018). This migration failure results in missing ganglion cells in affected segments of the colon. Affected colonic segments fail to relax, resulting in a functional pseudo-obstruction (Heuckeroth, 2018).

The majority of patients with HD have short-segment disease that involves the rectum and distal sigmoid colon (Wesson & Lopez, 2019a). Twenty percent of patients have long-segment disease in which the aganglionosis extends from the rectum to the proximal sigmoid colon (Wesson & Lopez, 2019a). Approximately 5% of patients have total colonic aganglionosis that involves the entire colon. The small bowel is rarely affected by HD. Short-segment HD generally carries the best prognosis.

The incidence of HD is about 1 in 5,000 live births with a male predominance (Best et al., 2014; Suita, Taguchi, Ieiri, & Nakatsuji, 2005). The recurrence rate in siblings is between 3% and 17%, depending on whether the HD is short or long segment. Several chromosomal abnormalities are associated with HD. These abnormalities include trisomy 21, Bardet–Biedl syndrome, cartilage-hair hypoplasia, congenital central hypoventilation syndrome, familial dysautonomia, multiple endocrine neoplasia type 2, Mowat–Wilson syndrome, Smith-Lemli-Opitz syndrome, and Waardenburg syndrome (Wesson & Lopez, 2019a). Genitourinary abnormalities, visual and hearing problems, congenital heart disease, and ARM may also be found in about 20% of patients with HD (Wesson & Lopez, 2019a).

Diagnosis

Most patients with HD are diagnosed within the first 2 months of life, while up to 10% of patients may not be diagnosed until childhood (Arshad, Powell, & Tighe, 2012). Bilious or nonbilious vomiting, abdominal distension, and failure to pass meconium within 48 hours of life are common clinical presentations that should raise the possibility of HD (Tabbers et al., 2014). While delayed meconium passage is a hallmark feature, a history of meconium passage within 48 hours of life does not fully exclude the possibility of HD. A forceful expulsion of stool and gas may be seen during digital rectal examination as the examining finger dilates the affected rectosigmoid segment. **Emergency Alert: Infants with HD may also present with enterocolitis that can progress to toxic megacolon if untreated. Clinical evidence of enterocolitis includes fever, vomiting, diarrhea, and persistent abdominal distension.**

Plain radiographs may show dilated bowel proximal to the aganglionic segments and an absence of gas in the rectosigmoid region. Contrast enema, anorectal manometry, and rectal biopsy are the three most common modalities for diagnosing HD. Rectal biopsy and anorectal manometry have the highest sensitivity and specificity of over 90%. Contrast enemas have sensitivities and specificities of 70% to 80% (Peranteau & Mattei, 2016). Selection of which test(s) to use may be dictated by institutional availability of equipment and expertise to interpret the results.

Initial evaluation often involves a contrast enema to look for a transition zone. In patients with short- or long-segment HD, the transition zone represents a change from a normal caliber or narrowed aganglionic rectum to a more dilated proximal colon (Peranteau & Mattei, 2016). In patients with total colonic aganglionosis, the colon may appear normal in size, but dilated loops of distal small bowel may be seen. The rectosigmoid index is the ratio between the diameter of the rectum and the sigmoid colon. In children without HD, this ratio is greater than 1, while in children with HD the ratio may be less than 1 (Garcia et al., 2007). A high false negative rate for HD limits its use as a gold standard examination. Suction rectal biopsy and anorectal manometry are considered more sensitive for diagnosing HD (Heuckeroth, 2018).

Anorectal manometry involves inserting a pressure transducer with a balloon at its tip into the rectum. As the balloon is inflated, the transducer continuously measures the pressure of the anal sphincter. Normally, inflation of the balloon should trigger a reflex relaxation of the anal sphincter. In patients with HD, this reflex anal relaxation is absent.

Rectal biopsy is performed to confirm the diagnosis of HD before surgical intervention. The procedure is performed by inserting a suction rectal biopsy instrument 2 to 3 cm into the rectum, applying negative pressure via an attached syringe to suction in intestinal mucosa into a side hole at the end of the device, and then triggering a blade within the biopsy device that excises a small piece of tissue (Noblett, 1969; Peranteau & Mattei, 2016). Samples should contain tissue that includes submucosa to be interpretable. The procedure is convenient, can be done at bedside, and does not require sedation or local analgesia. Uncommon complications include bacteremia, refractory bleeding, and bowel perforation (Peranteau & Mattei, 2016; Rees, Azmy, Nigam, & Lake, 1983). Histologic features of HD include absence of ganglion cells, hypertrophy of nerve fibers, and increased acetylcholinesterase staining (Peranteau & Mattei, 2016).

Management

Surgery is the definitive treatment for HD. Most surgery for HD is nonemergent. After fluid resuscitation, a NG or orogastric tube should be placed for intermittent or continuous suction, and broad-spectrum antibiotics should be started. Twice-daily rectal irrigations and daily digital rectal examinations are also used at some centers (Wesson & Lopez, 2019b). Surgery usually involves resection of the aganglionic portion of the colon and rectum followed by creation of a neorectum using ganglionated normal proximal bowel.

HD-associated enterocolitis is a form of severe infectious colitis unique to patients with HD that can occur before or after surgery (Wesson & Lopez, 2019b). Risk factors for enterocolitis include a family history of HD, trisomy 21, long-segment disease, and prior episodes of enterocolitis (Frykman & Short, 2012; Peranteau & Mattei, 2016). Common symptoms and signs of enterocolitis include abdominal distension, explosive diarrhea, vomiting, fever, lethargy, rectal bleeding, and shock (Frykman & Short, 2012; Peranteau & Mattei, 2016). Plain radiography with lateral decubitus or cross-table lateral views may show dilated proximal bowel, absence of air in the sigmoid or rectum, and air-fluid levels. Treatment of enterocolitis generally includes broad-spectrum antibiotics that target intestinal flora, rectal irrigation with normal saline, and fluid resuscitation. The patient should be kept NPO until there is evidence of clinical improvement or resolution of signs and symptoms. The duration of antibiotic treatment ranges from 5 to 14 days depending on the severity of the enterocolitis. Contrast enemas should be avoided in patients with enterocolitis due to the increased risk of intestinal perforation.

SMALL LEFT COLON

Background

Neonatal small left colon, also known as micro left colon, is characterized by uniform narrowing of the left colon from the splenic flexure to the anus. Neonatal small left colon is thought to be the result of functional immaturity of the colon (Ngo, Stanescu, & Phillips, 2018). There is dilatation of the colon proximal to the splenic flexure with a cone-shaped transitional zone between dilated and narrow areas.

Approximately 40% of patients with small left colon are infants of mothers with diabetes (Ngo et al., 2018). The exact cause of micro left colon is unknown but is thought to represent a colonic motility problem. Normal colonic motility is achieved at term by myenteric plexuses that innervate smooth muscles of the colon. These myenteric plexuses migrate to the colon in a cephalocaudal direction between 5 and 12 weeks of gestation; they mature to normal function as gestation progresses. Failure of migration leads to the absence of ganglion cells as observed in HD; immaturity of migrated myenteric plexuses leads to decreased motility and micro left colon. Histologic examination of the colon in such patients reveals morphologically immature plexuses.

Diagnosis

Infants with small left colon present with signs and symptoms of a lower intestinal obstruction, namely, abdominal distension, bilious vomiting, and failure to pass meconium. Plain radiographs of the abdomen reveal multiple gas-filled loops of dilated small bowel and proximal colon, with decreased air in the distal colon or rectum (Ngo et al., 2018). These features are indistinguishable from HD or meconium plug syndrome. Very rarely, significant distal obstruction with marked dilation proximally may lead to cecal perforation. Contrast enema (barium or Gastrografin) reveals a uniformly small left colon, cone-shaped transition zone in the splenic flexure, and dilated proximal colon (Ngo et al., 2018). HD may have similar findings. A distinguishing feature of micro left colon in contrast to HD is that following contrast enema, infants evacuate the contrast promptly and begin passing stools spontaneously with resolution of lower intestinal obstruction. In some cases, rectal biopsy may be needed to rule out HD. In micro left colon, rectal biopsy reveals the presence of ganglion cells, albeit immature; ganglion cells are absent in HD.

Management

Initial management is similar to that of any intestinal obstruction (diagnosed by plain radiographs): decompression by NG tube, maintenance of hydration, and correction of electrolyte imbalance. Contrast enema is both diagnostic and therapeutic. Oral feedings should be started as soon as the patient starts having bowel movements after an enema and gradually advanced as tolerated. The baby should be diligently monitored for abdominal distension, vomiting, or decreased stool, as these may be harbingers of the recurrence of obstruction. Small left colon spontaneously resolves in the neonatal period, and the long-term outlook is good with usually normal bowel movements.

MECONIUM ILEUS

Background

Meconium ileus (MI) is an obstruction of the distal ileum due to an accumulation of abnormally thick meconium (Carlyle, Borowitz, & Glick, 2012). In the past, a majority (almost 90%) of infants with MI were thought to have CF (Boczar, Sawicka, & Zybert, 2015). However, several studies have since reported 30% to 50% of children with MI do not have CF (Paradiso, Briganti, Oriolo, Coletta, & Calisti, 2011). Non-CF causes of MI include HD, prematurity, and low birth weight.

In CF patients, MI is the result of thick meconium, which in turn is the result of exocrine pancreatic insufficiency—a lack of hydrolytic enzymes results in meconium with an abnormally high content of protein and mucus glycoprotein, resulting in a very viscous meconium (Atlas & Rosh, 2016). It is also postulated that abnormally high fat content in the distal ileum increases neurotensin secretion, causing slowing of intestinal motility and resulting in MI (Carlyle et al., 2012). The histologic hallmark of MI is distension of the goblet cells of the intestinal mucosa.

Diagnosis

Neonates with MI usually present within the first 12 to 24 hours of life. The presentation of MI may be divided into two forms: simple or complicated. In simple MI, the distal ileum is obstructed by very viscid meconium, the proximal small bowel is dilated and thick-walled, and the colon is narrow and empty (microcolon). Complicated MI cases have additional features such as intestinal volvulus, atresia, necrosis, perforation, meconium peritonitis, and meconium pseudocyst.

Affected infants develop signs and symptoms of small bowel obstruction including abdominal distension, bilious vomiting, and absence of stool. Physical examination of the abdomen may reveal a doughy or putty-like ball of meconium that is movable. Rectal examination reveals a normal anal sphincter tone and an empty rectal vault without meconium or stool.

Plain radiographs may show a dilated proximal small bowel and a "soap bubble" or ground-glass appearance in the right lower quadrant (Ngo et al., 2018). Contrast enema shows microcolon. In complicated MI, plain radiographs may show ascites, peritoneal calcifications, or pneumoperitoneum. A sweat chloride test and DNA analysis for CF mutations should be done in all patients suspected of having MI; neonatal screening for CF may be helpful, but the lack of immediate results limits its usefulness in the first few days of life.

Management

The initial treatment is stabilizing the patient with respect to hydration and electrolytes. In simple MI, mildly hypertonic Gastrografin or Hypaque with acetylcysteine is delivered into the distal ileum (during contrast enema) under fluoroscopy to break up inspissated meconium (Carlyle et al., 2012). The loosened meconium is then passed by normal peristalsis. Maintaining adequate hydration is very important, as fluid from the intravascular space is drawn into the intestinal lumen with the hyperosmolar agent. Generally, 4 mL of half-normal saline solution is given for every 1 mL of retained enema. Surgery is indicated if the previous measures fail in simple MI or if the patient has complicated MI (Carlyle et al., 2012). Inspissated meconium is removed surgically by simple enterotomy. A temporary ileostomy may be needed in some cases.

Elemental formula feedings are started when intestinal function is deemed adequate. If the patient has CF, pancreatic enzymes should also be started with feedings. Pulmonary toilet should be initiated as soon as possible, and parents should be referred to a genetic counselor if CF is diagnosed. The long-term prognosis depends on the underlying etiology; non-CF patients have better outcomes than CF patients.

MECONIUM PLUG

Background

Meconium plug syndrome causes distal colonic obstruction and is caused by thick meconium; there is no pancreatic enzyme deficiency. Obstruction is relieved by the passage of meconium and there are no long-term consequences. It is important to distinguish meconium plug syndrome from HD and micro left colon.

The most likely cause of meconium plug syndrome is abnormal gut motility associated with immaturity or hypotonia; about 13% of

patients have HD (Keckler et al., 2008). Premature infants and infants with hypotonia are especially prone to developing a meconium plug. Infants of diabetic mothers are also at increased risk of developing a meconium plug, which is considered a variant of micro left colon.

Diagnosis

Meconium plug patients usually present with signs and symptoms of distal bowel/colonic obstruction; there is gradually increasing abdominal distension, bilious vomiting, and failure of meconium passage. Plain radiographs reveal multiple dilated small bowel loops. Contrast enema reveals a normal caliber colon (as compared to micro left colon) and dilated bowel proximal to the meconium plug.

Management

Supportive measures including NG tube for decompression and maintenance of hydration and electrolytes balance should be started as soon as possible after birth. Contrast enema usually results in dislodgement of the plug and relief from obstruction (Cuenca, Ali, Kays, & Islam, 2012). Once the plug is evacuated, distension has resolved, and normal intestinal function has returned, feedings can be started and advanced as tolerated. Rectal biopsy should be considered in all patients with meconium plug syndrome, especially if constipation continues after relief of the obstruction from the initial meconium plug. Overall, the prognosis is good and complete recovery is expected.

IMPERFORATE ANUS/ANORECTAL MALFORMATION

Background

ARM includes a spectrum of congenital malformations involving the anus and rectum; many are associated with a fistula between the rectum and urogenital system or between the rectum and perineum (Herman & Teitelbaum, 2012). ARM is thought to result from abnormal development of the urorectal septum, which separates the anorectum from the urogenital system, or failure of the migration of the anus. ARM may occur in isolation, as part of the VACTERL association, or other anomalies involving the sacrum, lower spinal cord, or kidneys (Bulas, 2018).

For clinical purposes, ARM is classified according to the lesion location in relation to the internal anal sphincter or levator ani muscle complex. In low lesions, the rectal pouch ends below the internal anal sphincter and opens into the perineum as a narrow opening (anal stenosis, type I) or a fistula (type II). In high lesions, the rectal pouch ends above the internal anal sphincter and communicates externally through a fistula (type III) to the urinary bladder, urethra, or vagina; in rare cases, there may not be any external communication (type IV), causing complete obstruction. In high lesions, the internal sphincter is either absent or very malformed, and there are associated sacral abnormalities. In both types of lesions, the external sphincter is almost always present.

The incidence of ARM in the general population is about 1 in 5,000 live births; it increases to 1 in 100 for siblings of affected individuals (Bischoff, Levitt, & Pena, 2016). The cause of abnormal urorectal septum development or arrested migration of the anus is not known. It seems, however, that both environmental and genetic factors are involved. The mildest form of low lesions presents as anal stenosis, where the anus and rectum are patent but very narrowed; the anus therefore looks very small; it may be missed, as the newborn may be able to pass pasty or loose stools. Other low lesions may be associated with a thin membrane covering the anal opening or a complete absence of an anal opening; in these cases, stool is passed through a fistula in the perineum. In high lesions, there is no anal opening and stool is passed with urine via a fistula to the bladder, urethra, or vagina.

Diagnosis

ARM presents with a variable degree of GI obstruction because of failed or incomplete passage of stool. Symptoms include abdominal distension, poor feeding, vomiting, and delayed or absent passage of meconium. In low lesions, perineal examination will reveal a very small anus or no discernible anal opening, ectopic anal opening, fistula, or bulge in the perineum. In high lesions, there is no anal opening or fistula externally; there may be stool mixed with urine or excreted from the vagina. Careful perineal examination is mandatory and diagnostic in identifying and categorizing ARM.

Management

The treatment of ARM depends on the nature of the defect; it is imperative to define low versus high lesions. As mentioned earlier, careful perineal examination is all that is needed for diagnosis. Prone cross-table lateral x-ray film at 12 to 16 hours after birth may reveal a dilated rectal pouch that ends blindly above the perineum, but it is unreliable for determining the level of the lesion; the larger the distance from the perineum (more than 1.5 cm), the more likely it is to be a high lesion. An ultrasound, CT, and MRI of the pelvis may be able to better define the level of the lesion, and one or more of these modalities may be used prior to a surgical approach.

A pediatric surgeon needs to be involved in the management of ARM as soon as the defect is identified. Anal stenosis (type I, low lesion) is treated by repeated anal dilation using Hegar dilators. The infant can be discharged once it is able to pass stool and there are no signs of obstruction; daily anal dilation is continued at home, as parents are trained prior to discharge. The other simple low lesion, where the anal opening is covered by a thin membrane, requires minimal surgical therapy. The membrane is ruptured or excised and repeated anal dilation is performed as previously noted.

Low lesions with a perineal fistula are corrected by posterior sagittal anorectoplasty, in which the rectal pouch is brought down through the external sphincter (identified using a nerve stimulator) and sutured to the skin at the anal opening. Any fistulous connection is removed. Postoperatively, the infant may need gentle rectal irrigation until stool passes. Anal dilation using the Hegar dilator is usually started after 2 weeks, depending on the pediatric surgeon, and continued at home.

High lesions may require complex reconstructive surgery. These patients have significant intestinal obstruction and require stabilization before surgery. Gastric decompression is achieved with NG tube placement, and dehydration or an electrolyte imbalance is rectified. Usually, correction of the defect is done in two stages. Initially a left-sided colostomy is done as soon as possible for decompression and fecal diversion. If there is any fistula, it is excised. In the second stage, definitive repair is accomplished in 3 to 12 months by abdominal perineal pull-through surgery, where the rectal pouch is pulled through the levator ani muscle sling and the external sphincter and the subsequent anastomosis is done at skin level. The timing of definitive surgery depends on adequate growth and nutritional status of the patient.

Postoperative care of neonates depends on the type of surgery performed. Care of anoplasty patients requires gentle cleaning with saline and monitoring for infection at the suture site and mucosal prolapse. Parents need to be trained in care of the wound site as well as possible dilation as needed. As there is a risk of recurrence of fistulas, patients should be observed for the passage of any stool mixed with urine and for any new opening in the perineum. Once the site is healed, feedings can be started. Initially, a stool softener

may be required to prevent formed stool. If the patient required a colostomy, then daily inspection of the colostomy is mandatory to ensure proper functioning and site integrity. Parents need to be trained in taking care of the colostomy.

All children with an imperforate anus should have an ultrasonography or MRI of the lumbosacral spinal cord to rule out tethering of the spinal cord. The urinary system should also be investigated by ultrasonography for any lesions.

The long-term outcome is measured in terms of achieving continence and a normal stool pattern. Patients with anal stenosis have a very good prognosis, and some may need stool softeners for a long time. For all other patients, there may be late complications, including rectocutaneous anastomosis stricture, recurrent rectourinary fistula, mucosal prolapse, constipation, and fecal incontinence. In general, children with low lesions (below the levator ani complex) achieve normal continence, while only a minority (about one-third) with high lesions achieve continence before school age. The overall mortality rate of patients with anorectal malformation is 15%; death is largely due to complex surgical intervention and is more likely from associated anomalies. About 75% of patients have good outcomes in achieving normal bowel movements and continence.

SUPPORT OF FAMILY WITH AN INFANT WITH A GI SYSTEM DISORDER

The birth of an infant with a congenital anomaly or one who is acutely ill elicits feelings of loss, guilt, and confusion for parents. Nurses and other health professionals must expect grief reactions and be prepared to help the family cope with the crisis. Strategies to cope include support for early contact between parents and infant and open lines of communication to provide factual information of the infant's condition and plan of care. Healthcare providers also need to patiently reinforce information on an ongoing basis as the family begins to process and accept the diagnosis. Understanding of the disease process is essential for parents to cope with the prognosis and ongoing healthcare needs. Encourage the parents to hold their infants to provide skin-to-skin (kangaroo) care as early as possible. Encourage them to express their concerns before they are discharged home.

SUMMARY

The GI system is vital to human growth and development and ultimately long-term survival. The vast majority of conditions that cause GI dysfunction in the infant are the result of congenital anatomic malformations. Additionally, any condition or situation that leads to ischemia and bacterial overgrowth places an infant at risk for NEC and resultant long-term sequelae. The input and support of a variety of nursing, medical, and other specialists are required for optimal outcomes of the infant's physiologic well-being and the parents' psychosocial stability. The major purposes of this chapter were to present the embryologic development of the GI tract and resultant anatomic structure and to describe common causes of neonatal dysfunction with implications for care.

CASE STUDY

■ Identification of the Problem.

An 18-day-old, 38 weeks' gestation male infant presented to the ER with history of poor feeding, poor stooling pattern, abdominal distention, and listlessness. He was admitted with a diagnosis of failure to thrive and had an orogastric tube placed and Pedialyte started. He was transferred to a tertiary care NICU for inability to establish IV access.

■ Assessment: History and Physical Examination

- 38-week gestation male infant born by normal spontaneous vaginal delivery (NSVD) to a 28-year-old, G4, P3003 mother who had an unremarkable pregnancy. Serologies negative, BW 3,220 g and Apgar scores of 8 at 1 minute and 9 at 5 minutes of life
- At birth admission, infant required observation in the hospital for failure to stool. A contrast enema on day of life (DOL) 2 showed movable stool in the colon and no anatomic problems. He was discharged home on DOL 4 after passing two stools.
- On DOL 16, his mother brought him to the hospital because he was irritable, lethargic, and feeding poorly. He was evaluated and sent home.
- On DOL 18, he presented to the ER with listlessness and abdominal distention and was admitted for failure to thrive. Weight at admission was 2,930 g. Unable to secure IV access, he was transferred to a NICU.
- Vital signs: Temp 37, HR 147, respiratory rate (RR) 40, BP 86/55 67, CRT 2 seconds, abdominal girth 36 cm

Physical examination on admission to the NICU:

- GENERAL: irritable active infant with good perfusion, slightly pale, OG tube in place
- HEENT: anterior fontanel soft, flat with sutures approximated, eyes clear with + red reflex
- CARDIOVASCULAR: RRR, no murmur noted, pulses 2+ and equal
- RESPIRATORY: on room air with bilateral clear breath sounds
- ABDOMEN: grossly distended, tender to the touch, BS audible, anus is patent and normally placed
- GENITOURINARY: normal male genitalia
- NEUROLOGIC: lethargic, irritable

Evaluation after transfer to NICU included laboratory work with electrolytes, CBC/differential, C-reactive protein (CRP), blood culture. Peripheral IV placed and PN and antibiotics were started. A Replogle tube was placed to low constant wall suction.

■ Differential Diagnosis

- Hirschsprung's disease
- Jejunoileal atresia
- Meconium ileus
- Meconium plug syndrome
- Small left colon syndrome

■ Diagnostic Tests

Laboratory Tests:

- CBC/differential: WBC 7.5, segmented cells 10, bands 24, hematocrit 45, platelet 326,000/mm^3
- CRP: 11.7
- Electrolytes WNL
- Blood cultures remained negative

Imaging Tests:

- Contrast enema DOL 2: showed movable stool in the colon and no anatomic problems
- Abdominal radiographs: revealed extremely gaseous, distended bowel with no air in the rectum

- Contrast enema (repeated secondary to no rectal air): normal-caliber colon with a transition zone noted at the level of the mid- to distal descending colon
- Rectal biopsy: absence of ganglion cells

HD presents similar to jejunoileal atresia, MI, meconium plug syndrome, and small left colon syndrome. A contrast enema can be helpful in diagnosing the disease by determining the caliber of the colon. Microcolon is typically seen with jejunoileal atresia and MI. Normal or enlarged colon is seen with HD, meconium plug, and small left colon syndrome. Retention of contrast material 24 hours after examination is suggestive of HD. Final diagnosis can be made by rectal biopsy through the anus with histologic examination of the specimen. Absence of ganglion cells in the submucosa confirms the diagnosis of HD.

■ Working Diagnosis

- Term infant with HD: based on absence of ganglion cells
- Colitis due to tender abdomen
- Clinical sepsis due to elevated CRP, shifted CBC, and lethargy

■ Development of Management Plan

- Gastric decompression
- Maintenance fluid support
- Continuous monitoring of vital signs and abdominal girth every 6 hours
- Antibiotics
- Surgical consult

■ Implementation and Evaluation of Effectiveness

Implementation of Management Plan

- Gastric decompression was initiated immediately.
- IV access was obtained on admission.
- PN started for total fluid volume ~ 140 to 150 mL/kg/day, AA at 3 g/kg/day, IL at 3 g/kg/day.
- Laboratory work sent for sepsis workup and electrolytes.
- Ampicillin, gentamicin, and Flagyl were started.
- Abdominal radiograph was obtained.
- Electrolytes were obtained daily until stable, then every 2 to 3 days.
- CBC/diff obtained daily until WNL, then PRN.
- Pediatric surgery consulted and performed normal saline enemas until surgery could be performed.
- After diagnostic workup was completed, decision made to attempt colon endorectal pull-through, although family was informed that a colostomy may be necessary if sequential histologic examinations made during surgery showed higher colonic involvement.
- Social work services was consulted to provide support to family.

Effectiveness of Management Plan

- Abdominal girth improved within 2 hours.
- A laparoscopic subtotal proctocolectomy–right colon endorectal pull-through was successfully performed.
- Ventilated 3 days postoperatively and then successfully extubated to room air.
- Ampicillin and gentamicin were discontinued postoperatively.
- Treated with Rocephin and Flagyl for 5 days postoperatively and will be discharged home on Flagyl for 1 to 2 months.
- Pain was controlled with morphine and Ativan PRN.
- PN was provided at 140 mL/kg/day with 3 g/kg/day protein and intralipids at 3 g/kg/day.
- Enteral feeds were begun on the fifth postoperative day and advanced slowly with full feeds reached in 4 days.

■ **Outcome.** He was discharged to home on room air, on full feedings, and Flagyl. Follow-up was with his pediatrician in 1 week and pediatric surgeon in 2 weeks after discharge.

EVIDENCE-BASED PRACTICE BOX

Establishing a timely diagnosis without adding to patient morbidity is a pillar of good medical practice. Ultrasonography is the preferred diagnostic test in several GI and non-GI conditions including pyloric stenosis, intussusception, cholelithiasis, hydronephrosis, ovarian cysts, and testicular torsion. The performance and interpretation of the majority of ultrasound examinations at most institutions rely on technicians and specialists who are not directly involved in the day-to-day care of patients. Depending on the institution, these individuals may or may not always be readily available.

Point-of-care ultrasonography (POCUS) is a bedside technology that allows healthcare providers to integrate clinical examination findings with real-time sonographic imaging (Marin et al., 2015). POCUS has several important advantages. First, the technology comes to the patients wherever they may be. Second, ultrasound and the performance of ultrasonography is one of the safest radiographic testing modalities. Finally, technologic innovations have dramatically improved portability and simplicity of use for POCUS (www.lumify.philips.com/web). While POCUS has been available since the 1990s, its clinical use in the realm of medical education and clinical practice has steadily increased only in recent years (Bornemann, Jayasekera, Bergman, Ramos, & Gerhart, 2018). Efforts are ongoing to define the conditions and diagnostic protocols for which POCUS can be used, and to develop training programs for nonspecialists who wish to use POCUS (Blanco & Volpicelli, 2016; Bornemann et al., 2018; Hoeffe, Desjardins, Fischer, Carriere, & Gravel, 2016). The use of POCUS in pediatrics is increasingly being recognized, paving the way for its implementation in training programs, and gradually into clinical practice (James, Alsani, Fregonas, Seguin, & Tessaro, 2016; Marin et al., 2015).

References

Blanco, P., & Volpicelli, G. (2016). Common pitfalls in point-of-care ultrasound: A practical guide for emergency and critical care physicians. *Critical Ultrasound Journal*, *8*, 15. doi:10.1186/s13089-016-0052-x

Bornemann, P., Jayasekera, N., Bergman, K., Ramos, M., & Gerhart, J. (2018). Point-of-care ultrasound: Coming soon to primary care? *The Journal of Family Practice*, 67(2), 70–74, 76–80. Retrieved

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EVIDENCE-BASED PRACTICE BOX (*continued*)

from https://www.mdedge.com/familymedicine/issue/157124/journal-family-practice-672

Hoeffe, J., Desjardins, M. P., Fischer, J., Carriere, B., & Gravel, J. (2016). Emergency point-of-care ultrasound in Canadian pediatric emergency fellowship programs: Current integration and future directions. *Canadian Journal of Emergency Medicine*, *18*(6), 469–474. doi:10.1017/cem.2016.20

James, V., Alsani, F. S., Fregonas, C., Seguin, J., & Tessaro, M. O. (2016). Point-of-care ultrasound in pediatric small bowel obstruction: An ED case series. *The American Journal of Emergency Medicine*, *34*(12), 2464.e1–2464.e2. doi:10.1016/j.ajem.2016.06.021

Marin, J. R., Lewiss, R. E., American Academy of Pediatrics—Committee on Pediatric Emergency Medicine, Society For Academic Emergency Medicine—Academy of Emergency Ultrasound, American College of Emergency Physicians—Pediatric Emergency Medicine Committee, and World Interactive Network Focused On Critical Ultrasound. (2015). Point-of-care ultrasonography by pediatric emergency medicine physicians. *Pediatrics*, *135*(4), e1113–e1122. doi:10.1542/peds.2015-0343

PARENT VOICES

Laurel Kapferer, MS

Our son Grayson was born via emergency C-section at 34 weeks. He had suffered IUGR, and at the time of his birth, he weighed only 2 lb 14 oz. Grayson was a very curious, aware, feisty baby with a larger than life personality. He would always interact with us and enjoyed skin-to-skin contact, being sung to, stories, his binky, and having his head rubbed gently.

During the first few days in the NICU, Grayson was progressing well. He was breathing on his own and regulating his own temperature. We thought for sure he would be home in no time. All that changed when Grayson was 6 days old. His color became pale and ashy, and his personality was completely different. That entire day he was crying and fussy. Nothing would comfort him. Later on in the day, Grayson developed a small pink area on his abdomen; x-rays later that day confirmed that he had developed necrotizing enterocolitis. Very quickly, his abdomen became distended and purple. He was eventually transferred to another hospital where his condition continued to worsen. His disease quickly progressed; we were told that Grayson's blood would not clot and surgery would not be possible. Eventually, Grayson's intestines were perforated which led to sepsis.

My husband and I held our son in our arms as he took his last breaths. Less than 18 hours after Grayson was diagnosed with NEC, he lost his life. This disease progressed rapidly and before we even could understand what it was, our son was gone.

Every moment that parents have with their children is precious, especially in the NICU. Things can turn around so quickly and there is not always a happy ending. It is so critical that as nurses you do everything you can to support families bonding with their babies, and that you help them create special moments to hold onto. When we knew that Grayson was losing his battle, we were able to get hand and foot prints, a lock of hair, pictures. In the end, those items along with his blankets, hats, binkies, bracelets, and our memories are all we have left of our son. In those times where it is clear that a child may not be making it home, please be mindful not to throw anything away. Instead, hold on to it for the family. We are so grateful that the NICU nurses thought to do this for us. Having items that were Grayson's, that he touched, and in some way connected with, mean the world to us now.

Jennifer M. Driscoll

Our daughter, Lilian Hope, was born 7 weeks premature, weighing only 2 lb 12 oz and 15 inches long. Lily's lungs were her main problem, as they are for many preemies, because the lungs are the last thing to develop. On the day she was born, she was doing well but still needed a CPAP machine to help her breathe. As the day progressed, her condition worsened. She was given nitric oxide, put onto a ventilator to breathe for her, and an oscillator to vibrate the lungs to help the flow of oxygen. Due to the force of the ventilator and oscillator, an air sac in her lungs burst and she had a chest tube inserted. Additionally, she had an erratic blood pressure and jaundice, and needed multiple blood transfusions. But the miracle continued as she began to gain strength inside herself; she came off the oscillator after 7 days and took out the ventilator herself. By day 8, we were able to hold her for the first time. She ended up only needing to stay in the NICU at Lehigh Valley Hospital for 24 days and was able to come home at a mere 3 lb 11 oz.

Aside from Lily's lung issues at birth, Lily suffered with severe GI issues from the time she was discharged from the NICU until age 5. Lily was bottle-fed because my milk never came in. This was beneficial for her in some ways because we were able to monitor how much she was eating and supplement with high-calorie formula and formula

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that was geared toward preemies. Unfortunately for her, she would have severe vomiting and lose what seemed like an entire bottle, often during a feeding, or just after she was done, and it would literally fly from her mouth across the room with very severe force. We saw many specialists because she would experience discomfort with the reflux, but it was hard to keep giving this tiny, fragile baby so much medication. Finally, once she began some solid foods, the reflux slowed down; however, it immediately led to other motility issues for her. Over her next few years, she would experience failure to thrive, worsened motility issues, and an eventual emergency surgery at Children's Hospital in Philadelphia. It took her one full year under the care of a specialist to work through those issues and begin to stabilize, which was by age 5.

ONLINE RESOURCES

Boston Children's Hospital. (n.d.). Esophageal atresia. Retrieved from http://www.childrenshospital.org/conditions-and-treatments/conditions/e/esophageal-atresia

Boston Children's Hospital. (2012). *Esophageal atresia–Foker process–Pediatric Playbook* [Video]. Retrieved from https://www.youtube.com/watch?v=bD3GTO3BiiYGastro Kids

Centers for Disease Control and Prevention. (n.d.). Handwashing: Clean hands save lives. Retrieved from https://www.cdc.gov/handwashing/when-how-handwashing.html

Children's Hospital Los Angeles. (n.d.). *Necrotizing enterocolitis*. Retrieved from https://www.chla.org/necrotizing-enterocolitis

REFERENCES

Abbasoğlu, L., Gün, F., Salman, F. T., Celik, A., Unüvar, A., & Görgün, O. (2003). The role of surgery in intraabdominal Burkitt's lymphoma in children. *European Journal of Pediatric Surgery, 13*, 236. doi:10.1055/s-2003-42242

Abdullah, F., & Karim, O. (2018). *BMJ Best Practice: Intestinal malrotation*. London, England: BMJ Publishing Group.

Abu Jawdeh, E. G., & Martin, R. J. (2013). Neonatal apnea and gastroesophageal reflux (GER): Is there a problem? *Early Human Development, 89*(Suppl. 1), S14–S16. doi:10.1016/s0378-3782(13)70005-7

Andorsky, D. J., Lund, D. P., Lillehei, C. W., Jaksic, T., Dicanzio, J., Richardson, D. S., . . . Duggan, C. (2001). Nutritional and other postoperative management of neonates with short bowel syndrome correlates with clinical outcomes. *The Journal of Pediatrics, 139*, 27–33. doi:10.1067/mpd.2001.114481

Applegate, K. E. (2009). Evidence-based diagnosis of malrotation and volvulus. *Pediatric Radiology, 39* (Suppl. 2), S161–S163. doi:10.1007/s00247-009-1177-x

Arbizu, R. A., Aljomah, G., Kozielski, R., Baker, S. S., & Baker, R. D. (2014). Intussusception associated with adenovirus. *Journal of Pediatric Gastroenterology and Nutrition, 59*, e41. doi:10.1097/mpg.0b013e3182868971

Arshad, A., Powell, C., & Tighe, M. P. (2012). Hirschsprung's disease. *British Medical Journal, 345*, e5521. doi:10.1136/bmj.e5521

Ashley, L. M., Allen, S., & Teele, R. L. (2001). A normal sonogram does not exclude malrotation. *Pediatric Radiology, 31*, 354. doi:10.1136/bmj.e5521

Atlas, A. B., & Rosh, J. R. (2016). Hirschsprung's disease. In R. Wyllie, H. S. Hyams, & M. Kay (Eds.), *Pediatric gastrointestinal and liver disease* (5th ed., pp. 999–1015). Philadelphia, PA: Elsevier.

Ballance, W. A., Dahms, B. B., Shenker, N., & Kliegman, R. M. (1990). Pathology of neonatal necrotizing enterocolitis: A ten-year experience. *The Journal of Pediatrics, 117*(1 Part 2), S6–S13. doi:10.1016/s0022-3476(05)81124-2

Barrett, K. E. (2014). *Gastrointestinal physiology*. New York, NY: McGraw-Hill.

Bautista, J., Fullerton, H., Briseno, M., Cui, H., & Fass, R. (2004). The effect of an empirical trial of high-dose lansoprazole on symptom response of patients with non-cardiac chest pain—a randomized, double-blind, placebo controlled, crossover trial. *Alimentary Pharmacology and Therapeutics, 19*(10), 1123–1130. doi:10.1111/j.1365-2036.2004.01941.x

Belza, C., Wales, J. C., Courtney-Martin, G., da Silva, N., Avitzur, Y., & Wales, P. W. (2017). An observational study of Smoflipid® versus Intralipid® on the evolution of parenteral nutrition associated liver disease in neonates with intestinal failure. *Transplantation, 101*(6 Suppl. 2), S95. doi:10.1097/01.tp.0000521424.13863.cc

Berseth, C. L., & Poenaru, D. (2005). Structural anomalies of the gastrointestinal tract. In H. W. Taeusch & D. Brodsky (Eds.), *Avery's diseases of the newborn* (8th ed., pp. 1086–1102). Philadelphia, PA: Saunders.

Best, K. E., Addor, M. C., Arriola, L., Balku, E., Barisic, I., Bianchi, F., . . . Rankin, J. (2014). Hirschsprung's disease prevalence in Europe: A register based study. *Birth Defects Research Part A: Clinical and Molecular Teratology, 100*, 695–702. doi:10.1002/bdra.23269

Best, K. E., Tennant, P. W., Addor, M. C., Bianchi, F., Boyd, P., Calzolari, E., . . . Rankin, J. (2012). Epidemiology of small intestinal atresia in Europe: A register-based study. *Archives of Disease in Childhood—Fetal and Neonatal Edition, 97*(5), F353–F358. doi:10.1136/fetalneonatal-2011-300631

Bhisitkul, D. M., Todd, K. M., & Listernick, R. (1992). Adenovirus infection and childhood intussusception. *Archives of Pediatrics and Adolescent Medicine, 146*, 1331–1333. doi:10.1001/archpedi.1992.02160230089026

Bischoff, A., Levitt, M. A., & Pena, A. (2016). Imperforate anus. In R. Wyllie, H. S. Hyams, & M. Kay (Eds.), *Pediatric gastrointestinal and liver disease* (5th ed., pp. 631–639). Philadelphia, PA: Elsevier.

BMJ Best Practice. (2017, July 7). Omphalocele and gastroschisis. Retrieved from https://bestpractice.bmj.com/topics/en-us/1158/pdf/1158.pdf

Boczar, M., Sawicka, E., & Zybert, K. (2015). Meconium ileus in newborns with cystic fibrosis—Results of treatment in the group of patients operated on in the years 2000–2014. *Developmental Period Medicine, 19*(1), 32–40. doi:10.1016/j.jcf.2017.06.007

Brandt, M. L. (2019). Intestinal malrotation in children. In J. I. Singer & M. B. Heyman (Eds.), *UpToDate*. Retrieved from https://www.uptodate.com/contents/intestinal-malrotation-in-children

Bruch, S. W., Kunisaki, S. M., & Coran, A. G. (2016). Congenital malformations of the esophagus. In R. Wyllie, H. S. Hyams, & M. Kay (Eds.), *Pediatric gastrointestinal and liver disease* (5th ed., pp. 232–240). Philadelphia, PA: Elsevier.

Bulas, D. I. (2018). Prenatal diagnosis of esophageal, gastrointestinal, and anorectal atresia. In D. Levine & L. Wilkins-Haug (Eds.), *UpToDate*. Retrieved from https://www.uptodate.com/contents/prenatal-diagnosis-of-esophageal-gastrointestinal-and-anorectal-atresia

Carlyle, B. E., Borowitz, D. S., & Glick, P. L. (2012). A review of pathophysiology and management of fetuses and neonates with meconium ileus for the pediatric surgeon. *Journal of Pediatric Surgery, 47*(4), 772–781. doi:10.1016/j.jpedsurg.2012.02.019

Chabra, S., & Gleason, C. A. (2005). Gastroschisis. *NeoReviews, 6*(11), e493–e499. doi:10.1542/neo.6-11-e493

Chan, C. F., & Wu, T. C. (2014). Recent advances in the management of pediatric intestinal failure. *Pediatrics and Neonatology, 55*, 426–430. doi:10.1016/j.pedneo.2013.11.005

Chao, H. C., & Vandenplas, Y. (2007). Comparison of the effect of a cornstarch thickened formula and strengthened regular formula on regurgitation, gastric emptying and weight gain in infantile regurgitation. *Diseases of the Esophagus, 20*(2), 155–160. doi:10.1111/j.1442-2050.2007.00662.x

Choong, C. K., & Beasley, S. W. (1998). Intra-abdominal manifestations of Henoch-Schönlein purpura. *Journal of Paediatrics and Child Health, 34*, 405–409. doi:10.1046/j.1440-1754.1998.00263.x

Corvaglia, L., Ferlini, M., Rotatori, R., Paoletti, V., Alessandroni, R., Cocchi, G., & Faldella, G. (2006). Starch thickening of human milk is ineffective in reducing the gastroesophageal reflux in preterm infants: A crossover study using intraluminal impedance. *The Journal of Pediatrics, 148*(2), 265–268. doi:10.1016/j.jpeds.2005.09.034

Craig, W. R., Hanlon-Dearman, A., Sinclair, C., Taback, S., & Moffatt, M. (2004). Metoclopramide, thickened feedings, and positioning for gastro-oesophageal reflux in children under two years. *Cochrane Database of Systematic Reviews*, (4), CD003502. doi:10.1002/14651858.cd003502.pub2

Cuenca, A. G., Ali, A. S., Kays, D. W., & Islam, S. (2012). "Pulling the plug"—Management of meconium plug syndrome in neonates. *Journal of Surgical Research, 175*(2), 33–46. doi:10.1016/j.jss.2012.01.029

D'Antiga, L., & Goulet, O. (2013). Intestinal failure in children: The European view. *Journal of Pediatric Gastroenterology and Nutrition, 56*(2), 118–126. doi:10.1097/mpg.0b013e318268a9e3

Davidson, G., Wenzl, T. G., Thomson, M., Omari, T., Barker, P., Lundborg, P., & Illueca, M. (2013). Efficacy and safety of once-daily esomeprazole for the treatment of gastroesophageal reflux disease in neonatal patients. *The Journal of Pediatrics, 163*, 692–698.e2. doi:10.1016/j.jpeds.2013.05.007

Devane, S. P., Coombes, R., Smith, V. V., Bisset, W. M., Booth, I. W., Lake, B. D., & Milla, P. J. (1992). Persistent gastrointestinal symptoms after correction of malrotation. *Archives of Disease in Childhood, 67*(2), 218–221. doi:10.1136/adc.67.2.218

deVries, P. A. (1980). The pathogenesis of gastroschisis and omphalocele. *Journal of Pediatric Surgery, 15*(3), 245–251. doi:10.1016/s0022-3468(80)80130-8

DiBaise, J. K., Young, R. J., & Vanderhoof, J. A. (2006). Enteric microbial flora, bacterial overgrowth, and short-bowel syndrome. *Clinical Gastroenterology and Hepatology, 4*(1), 11–20. doi:10.1016/j.cgh.2005.10.020

Eberly, M. D., Eide, M. B., Thompson, J. L., & Nylund, C. M. (2015). Azithromycin in early infancy and pyloric stenosis. *Pediatrics, 135*(3), 483–488. doi:10.1542/peds.2014-2026d

Feitz, R., & Vos, A. (1997). Malrotation: The postoperative period. *Journal of Pediatric Surgery, 32*(9), 1322–1324. doi:10.1016/s0022-3468(97)90312-2

Fonkalsrud, E. (2003). Rotational anomalies and volvulus. In J. A. O'Neill, J. Grosfeld, & E. Fonkalsrud (Eds.), *Principles of pediatric surgery* (2nd ed., p. 477). St. Louis, MO: Mosby.

Ford, E. G., Senac, M. O., Jr., Srikanth, M. S., & Weitzman, J. J. (1992). Malrotation of the intestine in children. *Annals of Surgery, 215*, 172–178. doi:10.1097/00000658-199202000-00013

Friedman, A. M., Ananth, C. V., Siddiq, Z., D'Alton, M. E., & Wright, J. D. (2016). Gastroschisis: Epidemiology and mode of delivery, 2005–2013. *American Journal of Obstetrics and Gynecology, 215*, 348.e1–348.e9. doi:10.1016/j.ajog.2016.03.039

Frykman, P. K., & Short, S. S. (2012). Hirschsprung-associated enterocolitis: Prevention and therapy. *Seminars in Pediatric Surgery, 21*, 328–335. doi:10.1053/j.sempedsurg.2012.07.007Garbi-Goutel, A., Brévaut-Malaty, V., Panuel, M., Michel, F., Merrot, T., & Gire, C. (2014). Prognostic value of abdominal sonography in necrotizing enterocolitis of premature infants born before 33 weeks gestational age. *Journal of Pediatric Surgery, 49*, 508. doi:10.1016/j.jpedsurg.2013.11.057

Garcia, R., Arcement, C., Hormaza, L., Haymon, M. L., Ward, W., Velasco, C., . . . Schmidt-Sommerfeld, E. (2007). Use of the recto-sigmoid index to diagnose Hirschsprung's disease. *Clinical Pediatrics, 46*(1), 59–63. doi:10.1177/0009922806289328

Goulet, O., Baglin-Gobet, S., Talbotec, C., Fourcade, L., Colomb, V., Sauvat, F., . . . Ricour, C. (2005). Outcome and long-term growth after extensive small bowel resection in the neonatal period: A survey of 87 children. *European Journal of Pediatric Surgery, 15*(2), 95–101. doi:10.1055/s-2004-821214

Goulet, O., & Ruemmele, F. (2006). Causes and management of intestinal failure in children. *Gastroenterology, 130*(2 Suppl. 1), S16–S28. doi:10.1053/j.gastro.2005.12.002

Gregory, K. E., DeForge, C. E., Natale, K. M., Phillips, M., & Van Marter, L. J. (2011). Necrotizing enterocolitis in the premature infant: Neonatal nursing assessment, disease pathogenesis, and clinical presentation. *Advances in Neonatal Care, 11*(3), 155–164. Retrieved from https://www.nursingcenter.com/journalarticle?Article_ID=1175487&Journal_ID=675992&Issue_ID=1175386.

Grosfeld, J. L., & Rescorla, F. J. (1993). Duodenal atresia and stenosis: Reassessment of treatment and outcome based on antenatal diagnosis, pathologic variance, and long-term follow-up. *World Journal of Surgery, 17*(3), 301–309. doi:10.1007/BF01658696

Gura, K. M., Lee, S., Valim, C., Zhou, J., Kim, S., Modi, B. P., . . . Puder, M. (2008). Safety and efficacy of a fish-oil-based fat emulsion in the treatment of parenteral nutrition-associated liver disease. *Pediatrics, 121*, e678–e686. doi:10.1542/peds.2007-2248

Hackam, D. J., Upperman, J., Grikscheit, T., Wang, K., & Ford, H. R. (2019). Pediatric surgery. In F. Brunicardi, D. K. Andersen, T. R. Billiar, D. L. Dunn, L. S. Kao, J. G. Hunter, . . . R. E. Pollock (Eds.), *Schwartz's principles of surgery* (11th ed.). New York, NY: McGraw-Hill. Retrieved from http://accessmedicine.mhmedical.com/content.aspx?bookid=2576&sectionid=216211209

Haeusler, M. C., Berghold, A., Stoll, C., Barisic, I., & Clementi, M. (2002). Prenatal ultrasonographic detection of gastrointestinal obstruction: Results from 18 European congenital anomaly registries. *Prenatal Diagnosis, 22*, 616–623. doi:10.1002/pd.341

Hall, J. E., & Guyton, A. C. (2016). Gastrointestinal physiology. In J. E. Hall & A. C. Guyton (Eds.), *Guyton and Hall textbook of medical physiology* (13th ed., pp. 797–841). Philadelphia, PA: Elsevier.

Heine, R. G., Jordan, B., Lubitz, L., Meehan, M., & Catto-Smith, A. G. (2006). Clinical predictors of pathological gastro-oesophageal reflux in infants with persistent distress. *Journal of Paediatrics and Child Health, 42*, 134–139. doi:10.1111/j.1440-1754.2006.00812.x

Herman, R. S., & Teitelbaum, D. H. (2012). Anorectal malformations. *Clinics in Perinatology, 39*, 403–422. doi:10.1016/j.clp.2012.04.001

Heuckeroth, R. O. (2018). Hirschsprung disease—Integrating basic science and clinical medicine to improve outcomes. *Nature Reviews Gastroenterology and Hepatology, 15*, 152–167. doi:10.1038/nrgastro.2017.149

Heurn, L., Pakarinen, M., & Wester, T. (2014). Contemporary management of abdominal surgical emergencies in infants and children. *British Journal of Surgery, 101*, e24–e33. doi:10.1002/bjs.9335

Holman, R. C., Stoll, B. J., Clarke, M. J., & Glass, R. I. (1997). The epidemiology of necrotizing enterocolitis infant mortality in the United States. *American Journal of Public Health, 87*, 2026–2031. doi:10.2105/ajph.87.12.2026

Horvath, A., Dziechciarz, P., & Szajewska, H. (2008). The effect of thickened-feed interventions on gastroesophageal reflux in infants: Systematic review and meta-analysis of randomized, controlled trials. *Pediatrics, 122*(6), e1268–e1277. doi:10.1542/peds.2008-1900

Hughes, M. D., Nyberg, D. A., Mack, L. A., & Pretorius, D. H. (1989). Fetal omphalocele: Prenatal US detection of concurrent anomalies and other predictors of outcome. *Radiology, 173*(2), 371–376. doi:10.1148/radiology.173.2.2678251

Hunter, C. J., Upperman, J. S., Ford, H. R., & Camerini, V. (2008). Understanding the susceptibility of the premature infant to necrotizing enterocolitis (NEC). *Pediatric Research, 63*, 117–123. doi:10.1203/pdr.0b013e31815ed64c

Hwang, C. S., Chu, C. C., Chen, K. C., & Chen, A. (2001). Duodenojejunal intussusception secondary to hamartomatous polyps

of duodenum surrounding the ampulla of Vater. *Journal of Pediatric Surgery, 36*, 1073–1075. doi:10.1053/jpsu.2001.24757

Iacono, G., Vetrano, S., Cataldo, F., Ziino, O., Russo, A., Lorello, D., . . . Cavataio, F. (2002). Clinical trial with thickened feeding for treatment of regurgitation in infants. *Digestive and Liver Disease, 34*(7), 532–533. doi:10.1016/s1590-8658(02)80115-3

Iben, S., & Rodriguez, R. (2016). Neonatal necrotizing enterocolitis. In R. Wyllie, H. S. Hyams, & M. Kay (Eds.), *Pediatric gastrointestinal and liver disease* (5th ed., pp. 554–564). Philadelphia, PA: Elsevier.

Infantino, B. J., Mercer, D. F., Hobson, B. D., Fischer, R. T., Gerhardt, B. K., Grant, W. J., . . . Quiros-Tejeira, R. E. (2013). Successful rehabilitation in pediatric ultrashort small bowel syndrome. *The Journal of Pediatrics, 163*, 1361–1366. doi:10.1016/j.jpeds.2013.05.062

Jadcherla, S. R. (2002). Gastroesophageal reflux in the neonate. In C. L. Berseth (Ed.), *Clinics in perinatology: Recent advances in neonatal gastroenterology* (pp. 135–158). Philadelphia, PA: Saunders.

James, L. P. (2002). Pharmacology for the gastrointestinal tract. In C. L. Berseth (Ed.), *Clinics in perinatology: Recent advances in neonatal gastroenterology* (pp. 115–134). Philadelphia, PA: Saunders.

James, V., Alsani, F. S., Fregonas, C., Seguin, J., & Tessaro, M. O. (2016). Point-of-care ultrasound in pediatric small bowel obstruction: An ED case series. *The American Journal of Emergency Medicine, 34*(12), 2464.e1–2464.e2. doi:10.1016/j.ajem.2016.06.021

Kaufman, S. S. (2016). Short bowel syndrome. In R. Wyllie, H. S. Hyams, & M. Kay (Eds.), *Pediatric gastrointestinal and liver disease* (5th ed., pp. 405–417). Philadelphia, PA: Elsevier.

Kaufman, S. S., Atkinson, J. B., Bianchi, A., Goulet, O. J., Grant, D., Langnas, A. N., . . . Tzakis, A. G. (2001). Indications for pediatric intestinal transplantation: A position paper of the American Society of Transplantation. *Pediatric Transplantation, 5*(2), 80–87. doi:10.1034/j.1399-3046.2001.005002080.x

Keckler, S. J., St Peter, S. D., Spilde, T. L., Tsao, K., Ostlie, D. J., Holcomb, G. W., & Snyder, C. L. (2008). Current significance of meconium plug syndrome. *Journal of Pediatric Surgery, 43*(5), 896–898. doi:10.1016/j.jpedsurg.2007.12.035

Kim, J. H. (2018). Neonatal necrotizing enterocolitis: Management. In S. A. Abrams (Ed.), *UpToDate*. Retrieved from https://www.uptodate.com/contents/neonatal-necrotizing-enterocolitis-management

Kim, J. H. (2019a). Neonatal necrotizing enterocolitis: Clinical features and diagnosis. In S. A. Abrams (Ed.), *UpToDate*. Retrieved from https://www.uptodate.com/contents/neonatal-necrotizing-enterocolitis-clinical-features-and-diagnosis

Kim, J. H. (2019b). Neonatal necrotizing enterocolitis: Pathology and pathogenesis. In S. A. Abrams (Ed.), *UpToDate*. Retrieved from https://www.uptodate.com/contents/neonatal-necrotizing-enterocolitis-pathology-and-pathogenesis

Kimble, R. M., Harding, J., & Kolbe, A. (1997). Additional congenital anomalies in babies with gut atresia or stenosis: When to investigate, and which investigation. *Pediatric Surgery International, 12*, 565–570. doi:10.1007/bf01371900

Kovesi, T., & Rubin, S. (2004). Long-term complications of congenital esophageal atresia and/or tracheoesophageal fistula. *Chest, 126*(3), 915–926. doi:10.1378/chest.126.3.915

Kwatra, N., Shalaby-Rana, E., Narayanan, S., Mohan, P., Ghelani, S., & Majd, M. (2013). Phenobarbital-enhanced hepatobiliary scintigraphy in the diagnosis of biliary atresia: Two decades of experience at a tertiary center. *Pediatric Radiology, 43*(10), 1365–1375. doi:10.1007/s00247-013-2704-3

Lees, E. A., Miyajima, F., Pirmohamed, M., & Carrol, E. D. (2016). The role of *Clostridium difficile* in the paediatric and neonatal gut—A narrative review. *European Journal of Clinical Microbiology and Infectious Diseases, 35*, 1047–1057. doi:10.1007/s10096-016-2639-3

Llanos, A. R., Moss, M. E., Pinzon, M. C., Dye, T., Sinkin, R. A., & Kendig, J. W. (2002). Epidemiology of neonatal necrotising enterocolitis: A population-based study. *Paediatric and Perinatal Epidemiology, 16*(4), 342–349. doi:10.1046/j.1365-3016.2002.00445.x

Loots, C., Kritas, S., van Wijk, M., McCall, L., Peeters, L., Lewindon, P., . . . Omari, T. (2014). Body positioning and medical therapy for infantile gastroesophageal reflux symptoms. *Journal of Pediatric Gastroenterology and Nutrition, 59*(2), 237–243. doi:10.1097/mpg.0000000000000395

Louw, J. H. (1959). Congenital intestinal atresia and stenosis in the newborn: Observations on its pathogenesis and treatment. *Annals of the Royal College of Surgeons of England, 25*, 209–234.

Lüth, S., Teyssen, S., Forssmann, K., Kölbel, C., Krummenauer, F., & Singer, M. V. (2001). Fecal elastase-1 determination: 'Gold standard' of indirect pancreatic function tests? *Scandinavian Journal of Gastroenterology, 36*(10), 1092–1099. doi:10.1080/003655201750422729

Malcolm, W. F., Smith, P. B., Mears, S., Goldberg, R. N., & Cotten, C. M. (2009). Transpyloric tube feeding in very low birthweight infants with suspected gastroesophageal reflux: Impact on apnea and bradycardia. *Journal of Perinatology, 29*(5), 372–375. doi:10.1038/jp.2008.234

Mandeville, K., Chien, M., Willyerd, F. A., Mandell, G., Hostetler, M. A., & Bulloch, B. (2012). Intussusception: Clinical presentations and imaging characteristics. *Pediatric Emergency Care, 28*, 842–844. doi:10.1097/pec.0b013e318267a75e

Manning, A. T., & Little, D. C. (2016). Intussusception in infants and children. In R. Wyllie, H. S. Hyams, & M. Kay (Eds.), *Pediatric gastrointestinal and liver disease* (5th ed., pp. 607–613). Philadelphia, PA: Elsevier.

Marin, J. R., Lewiss, R. E., American Academy of Pediatrics—Committee on Pediatric Emergency Medicine, Society For Academic Emergency Medicine—Academy of Emergency Ultrasound, American College of Emergency Physicians—Pediatric Emergency Medicine Committee, and World Interactive Network Focused On Critical Ultrasound. (2015). Point-of-care ultrasonography by pediatric emergency medicine physicians. *Pediatrics*, *135*(4), e1113–e1122. doi:10.1542/peds.2015-0343

McAteer, J. P., Ledbetter, D. J., & Goldin, A. B. (2013). Role of bottle feeding in the etiology of hypertrophic pyloric stenosis. *JAMA Pediatrics, 167*(12), 1143–1149. doi:10.1001/jamapediatrics.2013.2857

Mermel, L. A., Allon, M., Bouza, E., Craven, D. E., Flynn, P., O'Grady, N. P., . . . Warren, D. K. (2009). Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. *Clinical Infectious Diseases, 49*(1), 1–45. doi:10.1086/599376

Misra, S., Macwan, K., & Albert, V. (2007). Transpyloric feeding in gastroesophageal-reflux-associated apnea in premature infants. *Acta Paediatrica, 96*(10), 1426–1429. doi:10.1111/j.1651-2227.2007.00442.x

Moon, R. Y. (2011). SIDS and other sleep-related infant deaths: Expansion of recommendations for a safe infant sleeping environment. *Pediatrics, 128*(5), 1030–1039. doi:10.1542/peds.2011-2284

Morgan, D. R., Mylankal, K., el Barghouti, N., & Dixon, M. F. (2000). Small bowel haemangioma with local lymph node involvement presenting as intussusception. *Journal of Clinical Pathology, 53*, 552–553. doi:10.1136/jcp.53.7.552

Nakayuenyongsuk, W., Christofferson, M., Stevenson, D. K., Sylvester, K., Lee, H. C., & Park, K. T. (2018). Point-of-care fecal calprotectin monitoring in preterm infants at risk for necrotizing enterocolitis. *The Journal of Pediatrics, 196*, 98–103.e1. doi:10.1016/j.jpeds.2017.12.069

Nandivada, P., Carlson, S. J., Chang, M. I., Cowan, E., Gura, K. M., & Puder, M. (2013). Treatment of parenteral nutrition-associated liver disease: The role of lipid emulsions. *Advances in Nutrition, 4*, 711–717. doi:10.3945/an.113.004770

Nehra, D., & Goldstein, A. M. (2011). Intestinal malrotation: Varied clinical presentation from infancy through adulthood. *Surgery, 149*, 386–393. doi:10.1016/j.surg.2010.07.004

Neu, J., & Walker, W. A. (2011). Necrotizing enterocolitis. *New England Journal of Medicine, 364*, 255–264. doi:10.1056/nejmra1005408

Neu, J., & Weiss, M. D. (1999). Necrotizing enterocolitis: Pathophysiology and prevention. *Journal of Parenteral and Enteral Nutrition, 23*(5 Suppl.), S13–S17. doi:10.1177/014860719902300504

Ngo, A. V., Stanescu, A. L., & Phillips, G. S. (2018). Neonatal bowel disorders: Practical imaging algorithm for trainees and general radiologists. *American Journal of Roentgenology, 210*, 976–988. doi:10.2214/ajr.17.19378

Niedzielski, J., Kobielski, A., Sokal, J., & Krakós, M. (2011). Accuracy of sonographic criteria in the decision for surgical treatment in infantile hypertrophic pyloric stenosis. *Archives of Medical Science, 7*(3), 508–511. doi:10.5114/aoms.2011.23419

Noblett, H. R. (1969). A rectal suction biopsy tube for use in the diagnosis of Hirschsprung's disease. *Journal of Pediatric Surgery, 4*, 406–409. doi:10.1016/0022-3468(69)90606-x

Nylund, C. M., Denson, L. A., & Noel, J. M. (2010). Bacterial enteritis as a risk factor for childhood intussusception: A retrospective cohort study. *The Journal of Pediatrics, 156*, 761–765. doi:10.1016/j.jpeds.2009.11.026

Okamoto, T., Takamizawa, S., Arai, H., Bitoh, Y., Nakao, M., Yokoi, A., & Nishijima, E. (2009). Esophageal atresia: Prognostic classification revisited. *Surgery, 145*, 675–681. doi:10.1016/j.surg.2009.01.017

Olivé, A. P., & Endom, E. E. (2019). Infantile hypertrophic pyloric stenosis. In J. I. Singer & B. U. K. Li (Eds.), *UpToDate*. Retrieved from https://www.uptodate.com/contents/infantile-hypertrophic-pyloric-stenosis

Omari, T. I., Rommel, N., Staunton, E., Lontis, R., Goodchild, L., Haslam, R. R., Dent, J., & Davidson, G. P. (2004). Paradoxical impact of body positioning on gastroesophageal reflux and gastric emptying in the premature neonate. *The Journal of Pediatrics, 145*(2), 194–200. doi:10.1016/j.jpeds.2004.05.026

Orenstein, S. R., Hassall, E., Furmaga-Jablonska, W., Atkinson, S., & Raanan, M. (2009). Multicenter, double-blind, randomized, placebo-controlled trial assessing the efficacy and safety of proton pump inhibitor lansoprazole in infants with symptoms of gastroesophageal reflux disease. *The Journal of Pediatrics, 154*, 514–520. doi:10.1016/j.jpeds.2008.09.054

Orzech, N., Navarro, O. M., & Langer, J. C. (2006). Is ultrasonography a good screening test for intestinal malrotation? *Journal of Pediatric Surgery, 41*, 1005–1009. doi:10.1016/j.jpedsurg.2005.12.070

Pacilli, M., Spitz, L., Kiely, E. M., Curry, J., & Pierro, A. (2005). Staged repair of giant omphalocele in the neonatal period. *Journal of Pediatric Surgery, 40*, 785–788. doi:10.1016/j.jpedsurg.2005.01.042

Paradiso, V. F., Briganti, V., Oriolo, L., Coletta, R., & Calisti, A. (2011). Meconium obstruction in absence of cystic fibrosis in low birth weight infants: An emerging challenge from increasing survival. *Italian Journal of Pediatrics, 37*, 55. doi:10.1186/1824-7288-37-55

Peranteau, W. H., & Mattei, P. (2016). Hirschsprung's disease. In R. Wyllie, H. S. Hyams, & M. Kay (Eds.), *Pediatric gastrointestinal and liver disease* (5th ed., pp. 622–630). Philadelphia, PA: Elsevier.

Pergialiotis, V., Konstantopoulos, P., Karampetsou, N., Koutaki, D., Gkioka, E., Perrea, D. N., & Papantoniou, N. (2016). Calprotectin levels in necrotizing enterocolitis: A systematic review of the literature. *Inflammation Research, 65*(11), 847–852. doi:10.1007/s00011-016-0963-9

Phelps, S., Fisher, R., Partington, A., & Dykes, E. (1997). Prenatal ultrasound diagnosis of gastrointestinal malformations. *Journal of Pediatric Surgery, 32*, 438–440. doi:10.1016/s0022-3468(97)90600-x

Pironi, L., Arends, J., Baxter, J., Bozzetti, F., Peláez, R. B., Cuerda, C., . . . Shaffer, J. (2015). ESPEN endorsed recommendations. Definition and classification of intestinal failure in adults. *Clinical Nutrition, 34*, 171–180. doi:10.1016/j.clnu.2014.08.017

Putnam, P. E., Orenstein, S. R., Wessel, H. B., & Stowe, R. M. (1992). Tardive dyskinesia associated with use of metoclopramide in a child. *The Journal of Pediatrics, 121*, 983–985. doi:10.1016/s0022-3476(05)80357-9

Quirós-Tejeira, R. E., Ament, M. E., Reyen, L., Herzog, F., Merjanian, M., Olivares-Serrano, N., & Vargas, J. H. (2004). Long-term parenteral nutritional support and intestinal adaptation in children with short bowel syndrome: A 25-year experience. *The Journal of Pediatrics, 145*(2), 157–163. doi:10.1016/s0084-3954(07)70110-0

Ramaiah, R. N., Stevenson, M., & McCallion, W. A. (2005). Hypopharyngeal and distal esophageal pH monitoring in children with gastroesophageal reflux and respiratory symptoms. *Journal of Pediatric Surgery, 40*, 1557–1561. doi:10.1016/j.jpedsurg.2005.06.026

Rees, B. I., Azmy, A., Nigam, M., & Lake, B. D. (1983). Complications of rectal suction biopsy. *Journal of Pediatric Surgery, 18*, 273–275. doi:10.1016/s0022-3468(83)80098-0

Rosen, R., Vandenplas, Y., Singendonk, M., Cabana, M., DiLorenzo, C., Gottrand, F., . . . Tabbers, M. (2018). Pediatric gastroesophageal reflux clinical practice guidelines: Joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *Journal of Pediatric Gastroenterology and Nutrition, 66*(3), 516–554. doi:10.1097/mpg.0000000000001889

Ross, A. (2010). Acute abdominal pain. *Pediatrics in Review, 31*(4), 135–144. doi:10.1542/pir.31-4-135

Saller, D. N., Jr., Canick, J. A., Palomaki, G. E., Knight, G. J., & Haddow, J. E. (1994). Second-trimester maternal serum alpha-fetoprotein, unconjugated estriol, and hCG levels in pregnancies with ventral wall defects. *Obstetrics and Gynecology, 84*, 852–855. Retrieved from https://journals.lww.com/greenjournal/Abstract/1994/11000/Second_Trimester_Maternal_Serum_Alpha_.24.aspx

Salvatore, S., & Vandenplas, Y. (2016). Gastroesophageal reflux. In R. Wyllie, H. S. Hyams, & M. Kay (Eds.), *Pediatric gastrointestinal and liver disease* (5th ed., pp. 243–257). Philadelphia, PA: Elsevier.

Sato, T. T., & Chang, H. L. (2016). Abnormal rotation and fixation of the intestine. In R. Wyllie, H. S. Hyams, & M. Kay (Eds.), *Pediatric gastrointestinal and liver disease* (5th ed., pp. 640–647). Philadelphia, PA: Elsevier.

Schneider, J. G., & Oldham, K. T. (2016). Atresia and stenosis of the bowel. In R. Wyllie, H. S. Hyams, & M. Kay (Eds.), *Pediatric gastrointestinal and liver disease* (5th ed., pp. 648–653). Philadelphia, PA: Elsevier.

Seifarth, F. G., & Soldes, O. S. (2016). Congenital anomalies and surgical disorders of the stomach. In R. Wyllie, H. S. Hyams, & M. Kay (Eds.), *Pediatric gastrointestinal and liver disease* (5th ed., pp. 284–286). Philadelphia, PA: Elsevier.

Silva, C. T., Daneman, A., Navarro, O. M., Moore, A. M., Moineddin, R., Gerstle, J. T., . . . Epelman, M. (2007). Correlation of sonographic findings and outcome in necrotizing enterocolitis. *Pediatric Radiology, 37*, 274. doi:10.1007/s00247-006-0393-x

Sizemore, A. W., Rabbani, K. Z., Ladd, A., & Applegate, K. E. (2008). Diagnostic performance of the upper gastrointestinal series in the evaluation of children with clinically suspected malrotation. *Pediatric Radiology, 38*, 518–528. doi:10.1007/s00247-008-0762-8

Sondheimer, J. M., Cadnapaphornchai, M., Sontag, M., & Zerbe, G. O. (1998). Predicting the duration of parenteral nutrition after neonatal intestinal resection. *The Journal of Pediatrics, 132*, 80–84. doi:10.1016/s0022-3476(98)70489-5

Stamm, D. A., & Duggan, C. (2018). Management of short bowel syndrome in children. In C. Jensen & K. J. Motil (Eds.), *UpToDate*. Retrieved from https://www.uptodate.com/contents/management-of-short-bowel-syndrome-in-children

Stephenson, C. D., Lockwood, C. J., & MacKenzie, A. P. (2018). Omphalocele. In L. Wilkins-Haug & D. Levine (Eds.), *UpToDate*. Retrieved from https://www.uptodate.com/contents/omphalocele

Stephenson, C. D., Lockwood, C. J., & MacKenzie, A. P. (2019). Gastroschisis. In L. Wilkins-Haug & D. Levine (Eds.), *UpToDate*. Retrieved from https://www.uptodate.com/contents/gastroschisis

Struijs, M. C., Diamond, I. R., de Silva, N., & Wales, P. W. (2009). Establishing norms for intestinal length in children. *Journal of Pediatric Surgery, 44*, 933–938. doi:10.1016/j.jpedsurg.2009.01.031

St-Vil, D., Brandt, M. L., Panic, S., Bensoussan, A. L., & Blanchard, H. (1991). Meckel's diverticulum in children: A 20-year review. *Journal of Pediatric Surgery, 26*, 1289–1292. doi:10.1016/0022-3468(91)90601-o

Suita, S., Taguchi, T., Ieiri, S., & Nakatsuji, T. (2005). Hirschsprung's disease in Japan: Analysis of 3852 patients based on a nationwide survey in 30 years. *Journal of Pediatric Surgery, 40*, 197–202. doi:10.1016/j.jpedsurg.2004.09.052

Svenningsson, A., Svensson, T., Akre, O., & Nordenskjöld, A. (2014). Maternal and pregnancy characteristics and risk of infantile hypertrophic pyloric stenosis. *Journal of Pediatric Surgery, 49*(8), 1226–1231. doi:10.1016/j.jpedsurg.2014.01.053

Tabbers, M. M., DiLorenzo, C., Berger, M. Y., Faure, C., Langendam, M. W., Nurko, S., . . . Benninga, M. A. (2014). Evaluation and treatment of functional constipation in infants and children: Evidence-based

recommendations from ESPGHAN and NASPGHAN. *Journal of Pediatric Gastroenterology and Nutrition, 58*, 265–281. doi:10.1097/mpg.0000000000000266

Thompson, A. M., & Bizzarro, M. J. (2008). Necrotizing enterocolitis in newborns: Pathogenesis, prevention, and management. *Drugs, 68*(9), 1227–1238. doi:10.2165/00003495-200868090-00004

van der Zee, D. C., Tytgat, S. H. A., & van Herwaarden, M. Y. A. (2017). Esophageal atresia and tracheo-esophageal fistula. *Seminars in Pediatric Surgery, 26*, 67–71. doi:10.1053/j.sempedsurg.2017.02.004

Vandenplas, Y., Goyvaerts, H., & Helven, R. (1991). Gastroesophageal reflux, as measured by 24-hours pH-monitoring in 509 healthy infants screened for risk of sudden infant death syndrome. *Pediatrics, 88*, 834–840. Retrieved from https://pediatrics.aappublications.org/content/88/4/834

Vandenplas, Y., & Hassall, E. (2002). Mechanisms of gastroesophageal reflux and gastroesophageal reflux disease. *Journal of Pediatric Gastroenterology and Nutrition, 35*, 119–136. doi:10.1097/00005176-200208000-00005

Vandenplas, Y., & Sacre, L. (1987). Milk-thickening agents as a treatment for gastroesophageal reflux. *Clinical Pediatrics, 26*(2), 66. doi:10.1177/000992288702600202

Vo, N., & Sato, T. T. (2019). Intussusception in children. In J. I. Singer & B. U. K. Li (Eds.), *UpToDate*. Retrieved from https://www.uptodate.com/contents/intussusception-in-children

Walther, A. E., & Nathan, J. D. (2016). Newborn abdominal wall defects. In R. Wyllie, H. S. Hyams, & M. Kay (Eds.), *Pediatric gastrointestinal and liver disease* (5th ed., pp. 654–665). Philadelphia, PA: Elsevier.

Weinberger, E., Winters, W. D., Liddell, R. M., Rosenbaum, D. M., & Krauter, D. (1992). Sonographic diagnosis of intestinal malrotation in infants: Importance of the relative positions of the superior mesenteric vein and artery. *American Journal of Roentgenology, 159*, 825–828. doi:10.2214/ajr.159.4.1529850

Wesson, D. E. (2018). Intestinal atresia. In J. A. Garcia-Prats & M. B. Heyman (Eds.), *UpToDate*. Retrieved from https://www.uptodate.com/contents/intestinal-atresia

Wesson, D. E., & Lopez, M. E. (2019a). Congenital aganglionic megacolon (Hirschsprung disease). In J. I. Singer & B. U. K. Li (Eds.), *UpToDate*. Retrieved from https://www.uptodate.com/contents/congenital-aganglionic-megacolon-hirschsprung-disease

Wesson, D. E., & Lopez, M. E. (2019b). Emergency complications of Hirschsprung disease. In J. I. Singer & B. U. K. Li (Eds.), *UpToDate*. Retrieved from https://www.uptodate.com/contents/emergency-complications-of-hirschsprung-disease

Writing Committee for the American Lung Association Asthma Clinical Research Centers (2012). Lansoprazole for children with poorly controlled asthma: A randomized controlled trial. *Journal of the American Medical Association, 307*, 373–381. doi:10.1001/jama.2011.2035

Yee, W. H., Soraisham, A. S., Shah, V. S., Aziz, K., Yoon, W., & Lee, S. K. (2012). Incidence and timing of presentation of necrotizing enterocolitis in preterm infants. *Pediatrics, 129*, e298–e304. doi:10.1542/peds.2011-2022

Zenk, K. E., Sills, J. H., & Koeppel, R. M. (2003). *Neonatal medications and nutrition: A comprehensive guide* (3rd ed.). Santa Rosa, CA: NICU Ink.

Zimbric, G., Bonkowsky, J. L., Jackson, W. D., Maloney, C. G., & Srivastava, R. (2012). Adverse outcomes associated with gastroesophageal reflux disease are rare following an apparent life-threatening event. *Journal of Hospital Medicine, 7*, 476–481. doi:10.1002/jhm.1941

CHAPTER 9

Metabolic System

Susan Kau and Stephanie Hoe

INTRODUCTION

Metabolism is a sequence of chemical reactions that takes place in cells of the body. These reactions are responsible for the breakdown of nutrients and the generation of energy. Inborn errors of metabolism (IEM), also known as EM, are a group of disorders that causes blockages in metabolic pathways, which can lead to clinically significant consequences. Chemical compounds called enzymes are responsible for the reactions that happen to make metabolism. There are also cofactors, also known as compounds, that help these enzymes carry out their reactions. A few examples of metabolism include breaking down the carbohydrates, protein, and fats in food to release energy as well as transforming excess nitrogen into waste products that get excreted in urine.

EMs are a heterogenous group of monogenic diseases that can affect the metabolic pathways. Most EMs are named for an enzyme that is not working properly. Depending on the enzyme's job, its absence means toxic chemicals may build up, or an essential product may not be produced. The code or blueprint to produce an enzyme is usually contained on a pair of genes. Most people with inherited metabolic disorders inherit two defective copies of the gene—one from each parent. Both parents are carriers of the bad gene, meaning one normal copy and one defective copy. A mutation in the gene causes it to not function properly or not function at all. These can be inherited from their parents or occur spontaneously.

The likelihood that someone else in the family has the same EM depends on several factors:

- Inheritance pattern of EM
- Whether at-risk family member is a male or female
- Rest of family history (how many family members have previously been tested or diagnosed with disorder already)

When discussing how genetic conditions are passed on in a family, it is important to understand that we have two copies of most genes, with one copy inherited from our mother and one copy inherited from our father. This is not the case for genes that are on our sex chromosomes (the "X" and the "Y" chromosomes). These are different in men and women: men only have one X chromosome and therefore one copy of genes on that chromosome, while women have two X chromosomes and therefore two copies of genes on that chromosome. A father passes on his X chromosome to all his daughters and his Y chromosomes to all his sons. A mother passes on an X chromosome to each child. The recommendation is to talk to a metabolic specialist or genetics specialist for family members who may be at risk for having an EM and for coordination of genetic testing if deemed appropriate.

The earlier an infant develops symptoms of an EM, the more severe the disorder. Severity of symptoms is generally based on several factors: position of the defective enzyme within the metabolic pathway, whether or not there is any functional enzyme or cofactor being produced, and other genetic or environmental factors. EMs are considered multisystemic diseases and infants may present with a variety of symptoms dependent on the specific metabolic pathway. Symptoms of substrate and intermediary metabolism develop once a significant amount of toxic metabolites accumulates following the initiation of feeds and may include the following: poor feeding, vomiting, diarrhea, temperature instability, tachypnea, apnea, bradycardia, poor perfusion, irritability, involuntary movements, posturing, abnormal tone, seizures, and altered level of consciousness. For EM of energy deficiency, symptoms usually develop within 24 hours and are usually present at birth. Neonates with EMs that result in defects in energy production usually have dysmorphic features, skeletal malformations, cardiopulmonary compromise, organomegaly, and severe generalized hypotonia. For those infants with errors of substrate and intermediary metabolism, physical examination findings are usually unremarkable. Acute decompensation in the neonate includes certain forms of tyrosinemia, organic acidemia, urea cycle defects, fatty acid oxidation defects, and galactosemia. An infection in an infant with an EM can result in a metabolic crisis (McGuire, 2017). This condition can result in death but more research needs to be done in this area; a National Institutes of Health (NIH)-funded study *Metabolism, Infection, and Immunity in Inborn Errors of Metabolism* is being conducted by Dr. Peter McGuire. The inherited metabolic disorders manifesting in the early neonatal period are the focus of this chapter.

GENERAL PRINCIPLES: THE NEONATE WITH A METABOLIC DISORDER

Pathophysiology of EMs

The genetic mechanisms through which biochemical disease is inherited include autosomal dominant, autosomal recessive, sex-linked recessive, or a mutation in mitochondrial DNA

(Cederbaum, 2018). The genetic mutation leads to an absent or defective gene product or enzyme, causing either an accumulation of precursors before a blocked step in a metabolic pathway, a deficiency of a critical metabolic product, or both. In disorders involving the intermediary metabolism of small molecules (such as maple syrup urine disease, MSUD), the accumulated molecules give rise to an "intoxication syndrome" because of the profoundly toxic nature of these substances and their effect on the central nervous system (CNS). Disorders involving energy metabolism (such as pyruvate dehydrogenase, PDH, deficiency) lead to a failure of energy production or utilization with a broad range of symptoms and physiologic consequences. Other disorders, such as lysosomal storage diseases, involve complex molecules, and symptoms that arise from these disorders are permanent, progressive, and independent of intercurrent events.

Clinical Manifestations of EMs

Most neonates who are eventually diagnosed with EMs appear essentially normal at birth and have no history of antepartum or intrapartum complications. The placenta and maternal circulation protect the fetus from the damaging effects of toxins. Birth is followed by a symptom-free interval of variable duration. Some metabolic disorders are unmasked by the ingestion of formula, milk, or fructose. Others are unrelated to feeding or may be brought on by fasting, infection, or stress.

Metabolic disease in the newborn can be clinically silent, indolent, or acute (Cederbaum, 2018). Five common presentations have been described (Leonard & Morris, 2010):

- Neurologic presentation—acute encephalopathy, seizures, lethargy
- Hypoglycemia
- Acid–base abnormalities—particularly metabolic acidosis and respiratory alkalosis
- Cardiomyopathy and cardiac arrhythmias
- Acute liver disease

The earlier an infant develops symptoms of an EM, the more severe the disorder. Severity of symptoms is generally based on several factors: position of the defective enzyme within the metabolic pathway, whether or not there is any functional enzyme or cofactor being produced, or other genetic or environmental factors. EMs are considered multisystemic diseases and infants may present with a variety of symptoms depending on the specific metabolic pathway involved.

A complete family history should be obtained to determine if other individuals in the family have had similar symptoms or the same disorder, or if there is a history of unexplained infant death, sudden infant death syndrome (SIDS), mental retardation, or consanguinity (Leonard & Morris, 2010).

Diagnosis of EMs

The trigger for a metabolic workup varies with the situation. In infants initially suspected of having sepsis, a metabolic workup might be initiated when laboratory results to investigate infection fail to confirm infection. **Emergency Alert: Persistent metabolic acidosis with an increased anion gap, hypoglycemia, significant hyperammonemia, unexplained hepatic dysfunction, or ketonuria should always raise suspicion of EM** (Leonard & Morris, 2010). Although only a minority of EMs are associated with dysmorphism, the possibility of metabolic disease should not be discounted in the neonate with congenital malformations or unusual features.

The initial laboratory investigation of a suspected EM includes a broad range of tests of both blood and urine (Box 9.1). Nonspecific screening tests do not provide a diagnosis; at best, they will support a strong suspicion of a metabolic disorder and suggest a specific category of disease (e.g., organic acidemia, fatty acid oxidation disorders—FAOD). Interpretation of results can be tricky. Conditions of sampling can profoundly affect results. Blood and urine samples must be obtained prior to the initiation of therapy, and, whenever possible, both should be collected when the infant is symptomatic (Mussa, Porta, Hoffmann, & Sarafoglou, 2017). Extra blood and urine samples should be obtained and frozen for later testing. It is important for health professionals to understand

Box 9.1

GENERAL SCREENING TESTS FOR ERRORS OF METABOLISM

Blood Tests

Glucose
Complete blood count with differential
Blood gases
Electrolytes (and anion gap[a])

Liver function tests

Blood urea nitrogen and creatinine
Total and direct bilirubin
Prothrombin time and partial thromboplastin time
Uric acid
Ammonia
Lactate
Pyruvate
Amino acids
Free fatty acids
Ketones (3OH-butyrate, acetoacetate)
Creatinine phosphokinase
Newborn metabolic screen/blood acylcarnitine analysis
Cerebrospinal fluid glycine (to rule out nonketotic hyperglycinemia)

Urine tests

Glucose
Ketones
pH
Reducing substances
Ferric chloride reaction
Dinitrophenylhydrazine reaction
Amino acids
Organic acids
Odor
Orotic acid (if blood NH_4 elevated)

[a]Anion gap is (sodium − [chloride + bicarbonate]). Normal is less than 15 mEq/L.

the limitations of laboratory testing, which tests are appropriate under what conditions, and how the infant's symptoms relate to such testing (Rice & Steiner, 2016).

Quality and Safety: Secondary metabolic derangements can interfere with test interpretation, and biochemical abnormalities might be present only during acute episodes. Laboratory abnormalities can also be transient; a result within the reference range does not necessarily rule out a metabolic disorder. Studies may need to be repeated at specific times. Clinicians might be falsely reassured by screening tests that are inadequate to exclude certain conditions. Therefore, consultation with a metabolic specialist is recommended. Furthermore, a clinical history and as much information as possible about the infant's symptoms and the suspected diagnosis should be provided to the referral laboratory to improve the accuracy of testing and interpretation of results.

Postmortem Diagnosis. If a neonate with a possible metabolic disorder dies suddenly, it is of great importance to continue to try to establish the proper diagnosis for purposes of genetic counseling and future antenatal diagnosis. In addition to standard blood and urine samples, a sample of cerebrospinal fluid (CSF) should be obtained if possible, and whole blood and bile should be collected on filter paper. The routine state newborn screening card should be completed and sent. If the family declines a full autopsy, tissue biopsies should be obtained. Tissue samples of value are skin, liver, kidney, and muscle.

Neonatal Screening. Newborn screening was first introduced as a public health program in the United States in the early 1960s, and has expanded to other countries around the world, with different testing menus in each country. Both prenatal and newborn screenings have improved healthcare. The conditions included in the newborn screening programs around the world vary greatly, based on the legal requirements for screening programs, prevalence of certain diseases within a population, political pressure, and availability of resources for both testing and follow-up of identified patients.

The development of tandem mass spectrometry (MS/MS) has greatly improved the presymptomatic detection of a large number of EMs. With MS/MS, it is possible to measure 30 or 40 different metabolites in less than 2 or 3 minutes, using a single dried blood spot. MS/MS works by applying a charge to the compounds in solution, sending them through an electromagnetic field, sorting them out, and weighing them according to their mass-to-charge ratio. Expanded newborn screening using MS/MS is mandated in some states as part of the routine newborn screening program. It is also available to parents who wish to purchase it from a number of private laboratories at a nominal cost. Currently, MS/MS screens only for disorders of intermediary metabolism, including amino acid disorders, organic acid disorders, and FAODs. A normal neonatal screen, even an expanded newborn screen by MS/MS, does not rule out an error of metabolism in a suspicious clinical setting. **Quality and Safety: If newborn screening tests are still pending when a neonate manifests potential signs and symptoms of metabolic disease, clinicians should contact the screening laboratory promptly to determine whether a diagnosis can be provided or to expedite results** (Yudkoff, Summar, & Haberle, 2017).

Management of the Newborn With an EM

Treatment of EMs is tailored to the specific disorder once a diagnosis is made. In general, the goals of treatment are to minimize or eliminate the buildup of toxic metabolites that result from the block in the metabolic pathway while maintaining growth and development. This may be done by using diets, supplements, and medications.

As soon as it becomes apparent that the infant has some type of metabolic disorder, it is important to consult a metabolic specialist/geneticist. In addition to general supportive measures as indicated by the infant's symptoms, both general and specific treatments should be initiated. **Quality and Safety: Oral feedings and amino acid solutions (all protein sources) are withheld, and 10% glucose solution with electrolytes is administered temporarily until the precise diagnosis is ascertained.** A glucose infusion rate of at least 5 mg/kg/minute (and higher if tolerated, aiming for 120–150 kcal/kg/day) is administered, because many metabolic disorders are exacerbated by tissue catabolism (Cederbaum, 2018). **Quality and Safety: Intralipids are withheld until disorders of fatty acid oxidation have been ruled out. Acute hypoglycemia, metabolic acidosis, dehydration, hypovolemia, and electrolyte imbalances are corrected as part of the overall supportive management of a metabolic disorder. If the infant is to be transferred to a referral center, reliable vascular access should be secured prior to transport.** Hemodialysis or extracorporeal membrane oxygenation (ECMO) may be required for emergency management of some EMs. Liver transplantation can be lifesaving in some EMs. Many disorders with rapid neonatal or prenatal onset are lethal, and all that can be offered are palliative and symptomatic care.

Interactions with parents and other family members are critically important, not only at the time of diagnosis, but throughout the course of care (Box 9.2). EMs occur in newborn infants with a broad range of racial/ethnic backgrounds. It is important to provide culturally sensitive care, which includes access to interpreter services, exploration of the family's sociocultural background, and bidirectional communication as well as decision making in the best interest of the child (Stockler, Moeslinger, Herle, Wimmer, & Ipsiroglu, 2012).

UREA CYCLE DISORDERS

Urea cycle disorders (UCDs) are caused by inherited defects in genes encoding enzymes or membrane transporters involved in ureagenesis. All are transmitted as autosomal recessive traits except ornithine transcarbamylase (OTC) deficiency, which is X-linked, and the most common of the primary defects. In aggregate, the prevalence of UCDs is believed to be approximately 1 per 10,000 live births, if partial defects are included.

Box 9.2

NURSING IMPLICATIONS FOR FAMILIES OF INFANTS WITH ERRORS OF METABOLISM

Nurses should support the families of these infants in the following ways:

1. Assuring that the programs are implemented safely and effectively
2. Facilitating education of the nursing workforce, and developing and contributing to programs of research focused on newborn screening
3. Educating parents with appropriately timed discussion of results. Parental teaching that includes materials providing descriptions of how screening results will be communicated to the family and what they should expect if retesting is needed (Arnold et al., 2006; Davis et al., 2006).

Pathophysiology

The hepatic urea cycle is the mechanism used by the body to detoxify and eliminate ammonia generated from nitrogen waste. Five enzymatic reactions make up the urea cycle, leading to the incorporation of ammonia into urea and enabling its excretion in the urine (Figure 9.1). The first two steps, the carbamoyl phosphate synthetase (CPS) and OTC reactions, take place in the mitochondria and lead to the synthesis of citrulline. In a subsequent cytosolic reaction, citrulline is converted to argininosuccinate, which is hydrolyzed to arginine and fumarate. Arginine is then hydrolyzed to urea and ornithine is regenerated.

A block of the urea cycle can result from a deficiency of any one of the first five enzymes in the urea cycle pathway: carbamoyl phosphate synthetase I (CPSI deficiency), OTC deficiency, argininosuccinic acid synthetase (citrullinemia), argininosuccinic acid lyase (argininosuccinic aciduria), arginine, a cofactor producer, N-acetylglutamate synthase (NAGS) deficiency, or a transport protein (Yudkoff et al., 2017). The outcome of a block in the urea cycle is an accumulation of precursor metabolites, including ammonia, which have no effective alternate clearance pathway. The neonate, with an immature liver and tendency toward catabolism, is poorly equipped to handle the excess metabolites and rapidly succumbs to the neurotoxic effects of high ammonia levels. Hyperammonemic encephalopathy results from osmotic swelling in the brain caused by glutamine accumulation in cerebral astrocytes, where glutamine synthesis is increased in response to high ammonia levels. The developing brain is much more susceptible to the deleterious effects of excess ammonia than the adult brain, leading to irreversible cortical atrophy, ventricular enlargement, demyelination, or gray and white-matter hypodensities in survivors, the extent of which depends on the magnitude and duration of ammonia exposure and the degree of brain maturation (Braissant, 2010).

Clinical Manifestations

Infants with complete urea cycle enzyme defects such as OTC and CPSI deficiency are usually born at term, with no prenatal complications, because the maternal circulation prevents a buildup of toxic ammonia (Yudkoff et al., 2017). Affected newborns are initially healthy, but shortly after receiving their first protein feedings, they begin to show signs of clinical decompensation and hyperammonemic encephalopathy. **Emergency Alert: The earliest signs of ammonia toxicity are irritability, hypotonia, hypothermia, lethargy, poor feeding, vomiting, and hyperventilation.** A mild respiratory alkalosis with tachypnea is a common early finding that should prompt measurement of a plasma ammonia level. Neurologic deterioration is progressive, with loss of tone and reflexes, eventually leading to respiratory failure and coma. Hepatomegaly may also be present. Without treatment, most infants will die from complications such as cerebral or pulmonary hemorrhage, or neurologic or cardiac problems.

Diagnosis

The hallmark of a UCD is an elevated blood ammonia level. A plasma ammonia level of 150 µmol/L (>260 mcg/dL) or higher in neonates, with a normal anion gap and a normal blood glucose level, is a strong indicator of a UCD (Yudkoff et al., 2017). The exception is arginase (ARG) deficiency, which does not typically cause a rapid rise in plasma ammonia level. A normal ammonia level in a healthy infant is less than 65 µmol/L. Blood sampling and handling techniques can affect results. Blood for ammonia levels should be collected by arterial or venous sampling and kept on ice, and plasma should be separated within 15 minutes of collection. Hemolysis, delayed processing, and exposure to room air can falsely elevate ammonia levels. Blood taken by capillary puncture

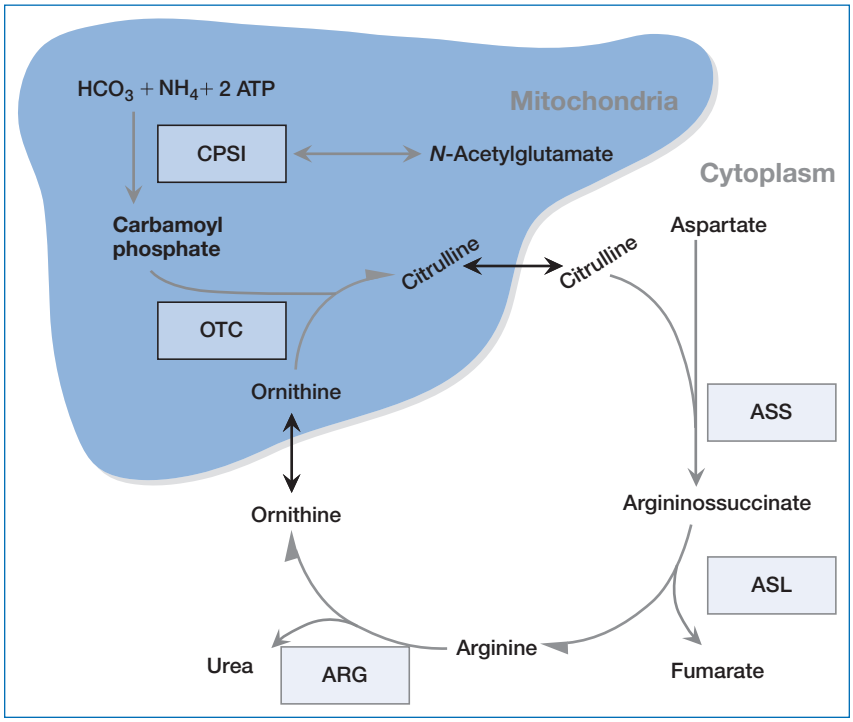

FIGURE 9.1 The urea cycle and alternative pathways of nitrogen excretion. Nitrogen is converted to ammonia (NH_4) and transported to the liver, where it is processed via the urea cycle, composed of five enzymes in the direct pathway: (1) carbamoyl phosphate synthetase I (CPSI); (2) ornithine transcarbamylase (OTC); (3) argininosuccinic acid synthetase (ASS); (4) argininosuccinic acid lyase (ASL); (5) arginase (ARG).

Source: Adapted from Ah Mew, N., Kimpson, K. L., Gropman, A. L., Lanpher, B. C., Chapman, K. A., & Summar, M. L. (2017). In M. P. Adam, H. H. Ardinger, R. A. Pagon, & S. E. Wallace (Eds.), *GeneReviews®* [Internet]. Seattle: University of Washington, Seattle. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK1217

is not appropriate for measurement of blood ammonia levels because of hemolysis (Leonard & Morris, 2010). If the ammonia level of a newborn with a suspected UCD is only modestly elevated, it should be repeated after several hours because the level can rise rapidly.

Blood gases, electrolytes, glucose, and other routine clinical laboratory tests should be obtained. Metabolic acidosis with a normal anion gap is sometimes present in UCDs, but not as often as in disorders of organic acid metabolism. Blood urea nitrogen (BUN) is low, but this is not specific or sensitive for UCDs. Liver function tests are important to rule out possible causes of hyperammonemia related to liver disorders or dysfunction (Merritt & Gallagher, 2018).

To arrive at a more precise diagnosis, quantitative plasma and urinary amino acids are necessary. Plasma glutamine, alanine, and asparagine, which serve as waste storage forms of nitrogen, may all be elevated. Plasma arginine is low in all UCDs of neonatal onset. The amounts of citrulline, argininosuccinic acid, and arginine in plasma and orotic acid in urine are usually sufficient to differentiate among UCDs. Measuring enzyme activity in tissue (liver, cultured skin fibroblasts, or RBCs) at a later point in time provides a definitive diagnosis that may be desirable for genetic counseling or future prenatal testing. Molecular genetic testing using linkage analysis or mutation scanning is available for OTC and CPSI deficiencies as well as citrullinemia, allowing for diagnostic confirmation, carrier detection, and prenatal diagnosis. Three UCDs (citrullinemia, argininosuccinate lyase deficiency, and ARG deficiency) can also be detected by the amino acid panels of expanded newborn screening programs employing MS/MS.

Differential Diagnosis of Hyperammonemia. Several other EMs can cause hyperammonemia in the newborn, notably the organic acidemias, propionic acidemia, methylmalonic acidemia (MMA), the FAODs, medium chain acyl-CoA dehydrogenase deficiency (MCAD), systemic carnitine deficiency, and long-chain FAODs, although the last group is also associated with hypoglycemia. Hyperammonemia is also a feature of pyruvate carboxylase deficiency (PCD) and PDH deficiency. In transient hyperammonemia of the newborn (THAN), very high plasma ammonia levels, often matching those of UCDs, exist for which no underlying cause can be found. THAN is usually associated with prematurity and has no genetic basis, nor does it recur in infants who survive the initial episode (Merritt & Gallagher, 2018). A simple algorithm can be useful to determine the cause of hyperammonemia (Figure 9.2).

The uniform newborn screening panel was updated to include more UCDs (U.S. Department of Health and Human Services [HHS], 2018). To date, no screening is available for OTC, CPS1, or NAGS deficiency.

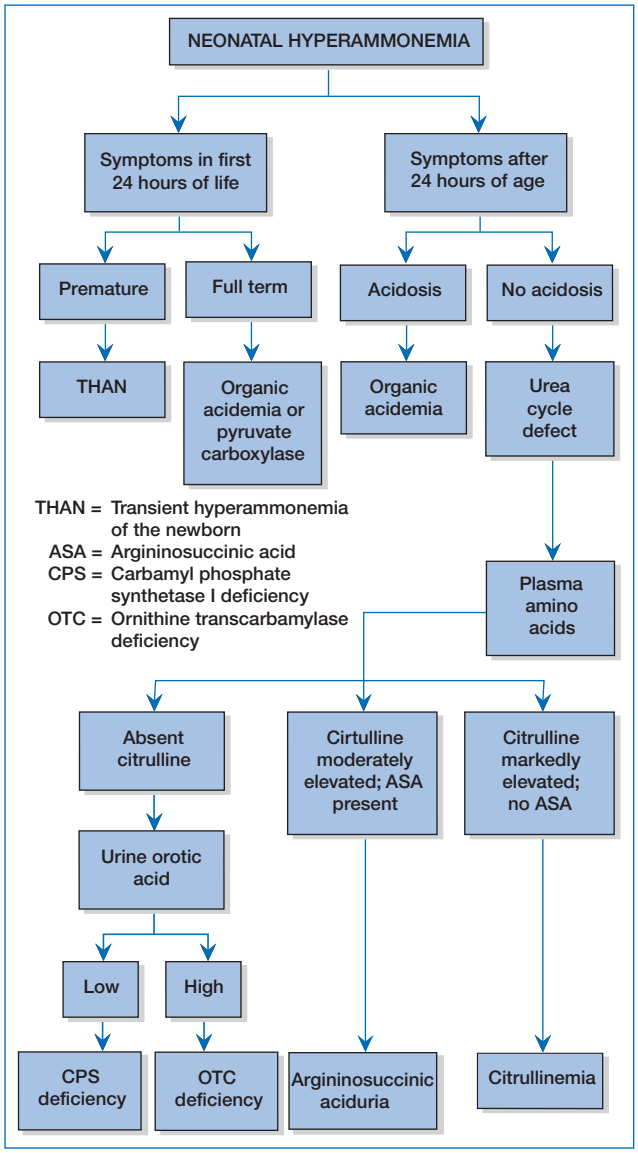

FIGURE 9.2 Algorithm to differentiate among conditions that produce neonatal hyperammonemia.

Source: Redrawn from Burton, B. K. (2000). Urea cycle disorders. *Clinics in Liver Disease, 4,* 815–830. doi:10.1016/S1089-3261(05)70143-4

Management

The emergency treatment of an infant with a suspected UCD has three simultaneous requirements: (1) physical removal of ammonia from the circulation; (2) reversal of catabolism; and (3) scavenging of excess nitrogen (Yudkoff et al., 2017). **Quality and Safety: Dietary protein intake should cease and be replaced by high-energy intake with a protein-free formula or by intravenous glucose and lipid infusion started, if enteral feeding cannot be tolerated.** Protein intake is stopped only temporarily, however, because failure to supply essential amino acids will eventually result in catabolism and further ammonia production. Within 48 hours, 1 to 1.5 g/kg/day of protein should be restarted, with 50% as essential amino acids. Fever, if present, must be aggressively treated. The kidneys remove ammonia poorly, so plasma ammonia levels are monitored closely and ammonia concentrations greater than 500 µmol/L must be reduced promptly with hemodialysis or hemofiltration. Peritoneal dialysis is much less effective in clearing ammonia from the body. For this reason, it is recommended that neonates with symptomatic hyperammonemia be transferred without delay to a neonatal facility capable of providing effective toxin removal.

Compounds that conjugate to amino acids, providing an alternate route for the excretion of nitrogen, can be given to lower the nitrogen burden, and therefore the ammonia burden, of an infant with a UCD. These agents (called "scavenger drugs" or diversion therapy) include N-carbamylglutamate (which activates CPSI and stimulates ureagenesis), sodium benzoate (which is conjugated with glycine to form hippurate), and sodium phenylbutyrate (which is oxidized in the liver to phenylacetate and then with glutamine and excreted in the urine). N-carbamylglutamate has been effectively used to treat NAGS deficiency (Daniotti, la Marca, Fiorini, & Filippi, 2011). Serum potassium levels must be monitored closely when these drugs are used. A preparation

combining both sodium phenylbutyrate and sodium benzoate is also available. In babies with citrullinemia and argininosuccinic aciduria, nitrogen can be excreted by increasing losses of citrulline and argininosuccinic acid, respectively. Arginine supplementation enhances the excretion of these metabolites by replenishing the supply of ornithine. However, high doses of the intravenous preparation L-arginine-HCl can cause metabolic acidosis and must be administered via central line because it can cause tissue necrosis if extravasation occurs.

A neonate in acute hyperammonemic coma caused by a suspected UCD should be given loading doses followed by continuous infusions of the ammonia-scavenging drugs (L-arginine-HCl, N-carbamylglutamate, sodium benzoate, and sodium phenylacetate), and drug levels should be monitored to reduce the risk for toxicity. Dietary protein is reintroduced in low amounts (0.5 g/kg/day) to encourage an anabolic state, while continuing diversion therapy to control ammonia levels. Alternative therapies that have been used with variable success for neonatal UCDs include liver and hepatocyte transplantation.

Prognosis. Even with the most vigorous intervention, UCDs of neonatal onset are often fatal, and the few survivors have a high rate of neurologic disability (Braissant, 2010). In a recent series, a mortality rate of 32% was found in infants with UCDs who were symptomatic within the first 30 days of life (Summar, Dobbelaere, Brusilow, & Lee, 2008). OTC deficiency is typically the most severe and lethal defect, particularly among males. The extent of permanent neurologic impairment in survivors is related to the duration of the hyperammonemic coma, plasma ammonia level at diagnosis, and other unidentified factors. Neonatal onset is associated with the worst prognosis (Braissant, 2010). Neurologic outcomes can be improved with early orthotopic liver transplantation (Campeau et al., 2010).

DISORDERS OF AMINO ACID METABOLISM

Amino acids play a role in literally all metabolic and cellular functions. As the constituents of protein, amino acids are used for the synthesis of new protein and as a source of carbon skeletons for generating glucose and ketone bodies. Amino acids are classified as nonessential or essential, depending on whether they can be synthesized by the body or must be obtained from dietary sources.

The disorders of amino acid metabolism, also called aminoacidopathies, arise from deficiencies of enzymes required to metabolize specific amino acids or amino acid transporters. The effects of the aberrant metabolism are highly disease specific. In some aminoacidopathies, clinical symptoms are caused by the relatively rapid accumulation of toxic metabolites that are substrates for the dysfunctional enzyme (Leonard & Morris, 2006). In other amino acid disorders, damaging effects of the enzyme deficiency are more gradual and chronic in nature.

The most well-known disorder of amino acid metabolism, perhaps of all the errors of metabolism, is phenylketonuria (PKU). The clinically and biochemically heterogeneous disorders of amino acid metabolism are inherited primarily as autosomal recessive traits.

Nonketotic Hyperglycinemia (NKH)

Pathophysiology. NKH (also known as glycine encephalopathy) is a disorder of glycine metabolism that is generally fatal in its neonatal form. Glycine, a glucogenic amino acid, is normally metabolized by a complex of enzymes known as the glycine cleavage complex, consisting of four proteins encoded on four different chromosomes. A defect in any of these enzymes interferes with the cleavage of glycine, resulting in a steep rise in glycine concentration in the blood and CSF. The exact pathophysiology of NKH is not known, but it is believed to be related to glycine's role as a neurotransmitter (Gibson, Van Hove, Willemsen, & Hoffman, 2017).

Clinical Manifestations. In classic neonatal NKH, symptoms usually start soon after birth and are not related to feedings. The clinical picture is dominated by neurologic decompensation: rapidly increasing stupor, lethargy, unresponsiveness, apnea, and sustained seizures that are difficult to control (Gibson et al., 2017). Myoclonic jerking and hiccupping (from diaphragmatic spasms) are also common. Within 1 to 3 days, the infant becomes comatose and death ensues. Babies who survive have intractable seizures and uniformly poor neurologic outcomes.

Diagnosis. Glycine is elevated in plasma, urine, and CSF. The CSF-to-plasma glycine concentration ratio of affected infants is greater than 0.09 (normal is <0.04). The diagnostic workup fails to find evidence such as metabolic acidosis, ketosis, hyperammonemia, or abnormal organic acids in blood or urine suggestive of another EM. Electroencephalographic (EEG) tracings typically show a burst suppression pattern with hypsarrhythmia (random, high-voltage slow waves and spikes that arise from multiple foci and spread to all cortical areas). Confirmation of the exact enzyme deficiency is made by enzyme assay of a liver sample or by molecular analysis.

Management. No consistently effective therapy has been discovered for classic neonatal-onset NKH. Attempts to reduce plasma glycine levels with sodium benzoate, and manage seizures with anticonvulsants, have not changed the poor neurodevelopmental outcomes of NKH (Gibson et al., 2017).

Hereditary Tyrosinemia

Hereditary tyrosinemia type I, also called hepatorenal tyrosinemia or fumarylacetoacetate hydrolase (FAH) deficiency, is a severe autosomal recessive metabolic disorder affecting the liver, kidney, and nervous system.

Pathophysiology. Tyrosine is derived from the metabolism of dietary phenylalanine, and from catabolic processes. Tyrosine degradation requires a series of enzymes, the last of which is FAH. A deficiency of this enzyme characterizes tyrosinemia type I (Morris & Chakrapani, 2017). The offending compounds in tyrosinemia type I are fumarylacetoacetate and maleylacetoacetate, both of which accumulate in the cells of the liver and kidney and cause cell death by apoptosis. Although hepatocytes are quickly regenerated, liver function can deteriorate rapidly in babies with tyrosinemia type I (Cederbaum, 2018).

Clinical Manifestations. Patients with hereditary tyrosinemia type I may come to clinical attention in the newborn period or within the first 3 weeks of life. Newborns present with evidence of liver dysfunction including firm hepatomegaly, splenomegaly, bleeding from coagulation defects, jaundice, and ascites (Morris & Chakrapani, 2017). Renal tubular dysfunction and hypophosphatemic rickets are common.

Diagnosis. The diagnostic workup includes liver function tests, which typically show elevated transaminases, and prolonged PT and PTT. Plasma tyrosine, phenylalanine, methionine, bilirubin, and serum alfa fetoprotein (AFP) may be elevated. The urine organic acid analysis reveals increased excretion of succinylacetone. The diagnosis can be confirmed by enzyme analysis of cultured skin fibroblasts or molecular studies. Hereditary tyrosinemia is included in the recommended uniform newborn screening panel (HHS, 2018).

Management. Hereditary tyrosinemia type I is now treated with nitisinone, a potent inhibitor of 4-hydroxyphenylpyruvate dioxygenase (Morris & Chakrapani, 2017). The response is monitored with urine succinylacetone, liver function tests, clotting studies, renal tubular function, and serum AFP. Most patients respond within a week with improved liver and renal function.

Dietary management involves feeding the infant a phenylalanine- and tyrosine-free formula, or breastfeeding, with phenylalanine supplementation sparingly, if needed (Morris & Chakrapani, 2017). Some infants will require a liver transplant to avoid the development of hepatocellular carcinoma.

Transient Tyrosinemia

Transient tyrosinemia in the newborn is the most common disorder of tyrosine metabolism.

Pathophysiology. Transient tyrosinemia is most likely caused by immaturity of 4-hydroxyphenylpyruvic acid dioxygenase (4HPPD), a vitamin C–dependent enzyme in the tyrosine degradation pathway. Risk factors include prematurity (hepatic immaturity), low vitamin C intake, and excessive protein intake. In some infants, transient tyrosinemia may be precipitated by endogenous catabolism. Tyrosinemia peaks in the first 14 days of life and resolves by 1 month of life (Morris & Chakrapani, 2017).

Clinical Manifestations. Lethargy and poor feeding may be seen in neonates with hypertyrosinemia, particularly in preterm infants.

Diagnosis. Transient hypertyrosinemia is identified by positive newborn metabolic screen.

Management. All infants with an elevated tyrosine on initial newborn screen should have a repeat screen done, with confirmatory testing for those who remain abnormal (see Hereditary Tyrosinemia). This is usually a self-limited disorder that does not require therapy. Therapies include a low-protein diet and supplemental vitamin C as a cofactor to increase the activity of 4HPPD and accelerate the fall in tyrosine concentration.

Phenylketonuria

Classic PKU is an autosomal recessive disorder caused by mutations in both alleles of the gene for phenylalanine hydroxylase, found on chromosome 12. Classic PKU occurs in about 1 in 10,000 to 13,000 live births (Hertzberg, Hinton, Therrell, & Shapira, 2011). Although PKU rarely manifests clinically in the newborn period, it is discussed here because it is important for neonatal caregivers to be able to provide accurate information to parents about key genetic conditions for which their newborn infants are being screened.

Pathophysiology. The effect of the inactive phenylalanine hydroxylase enzyme is an inability to metabolize phenylalanine, resulting in hyperphenylalaninemia. Following ingestion of adequate amounts of breast milk or formula, blood phenylalanine levels gradually increase. Phenylketonuric compounds are excreted in the urine, one of which (phenylacetic acid) imparts the musty or mousy odor characteristic of PKU. If dietary therapy is not implemented at birth, mental retardation can occur.

Clinical Manifestations. Biochemical manifestations of PKU are present in the newborn, but there are no outward clinical signs or symptoms. A musty odor may be detectable in the infant's urine around the end of the first week of life, if plasma phenylalanine levels reach 10 to 15 mg/dL.

Diagnosis. **Quality and Safety: Early diagnosis is critical because PKU is a preventable cause of mental retardation.** Plasma phenylalanine in the normal infant is less than 2 mg/dL. In infants with PKU, the plasma phenylalanine level usually exceeds 4 mg/dL by 24 hours of age and is 20 to 40 mg/dL by the end of the first week of life. PKU is a pioneer among metabolic disorders; it was the first disorder for which a screening test was developed in 1961 (the Guthrie test, a bacterial inhibition assay), and the first disorder to be screened for using MS/MS. MS/MS has dramatically decreased the number of false positive screening results, as well as further clarifying the prevalence of variants of hyperphenylalaninemia in the population.

Management. PKU is currently treated with a low-phenylalanine diet; however, compliance can be a long-term problem and dietary treatment can be associated with other nutritional deficiencies. Enzyme substitution with recombinant phenylalanine ammonia lyase is being explored as an alternative form of therapy (Cleary, 2010).

DISORDERS OF ORGANIC ACID METABOLISM

The organic acid disorders are disorders of intermediary metabolism resulting from a deficient enzyme or transport protein, the lack of which causes a block in a metabolic pathway. The block occurs in a step after deamination of the amino acid, and the resulting metabolites are organic acid derivatives. An organic acid is distinguished from an amino acid in that it contains no nitrogen. Because these disorders lead to an accumulation of organic acids in the urine, they are often referred to as "organic acidurias."

Maple Syrup Urine Disease

MSUD, a branched-chain organic aciduria, is a disorder resulting from one or more mutations in the gene encoding the enzymes that catalyze the branched-chain amino acids (BCAA) leucine, isoleucine, and valine. The name MSUD refers to the intensely sweet, maple sugar odor of the cerumen, skin, and urine that accompanies the disorder (Box 9.3). The incidence of MSUD is about 1 in 200,000 in the general population, but in the Old Order Mennonites of southeastern Pennsylvania the frequency is 1 in 358 births (Puffenberger, 2003).

Pathophysiology. The second common step in the degradation of a BCAA involves the enzyme branched-chain ketoacid dehydrogenase (BCKAD) complex. This enzyme catalyzes the conversion of the 3-ketoacid derivatives of the BCAA into their decarboxylated coenzyme metabolites within the mitochondria (Hoffmann, Burlina, & Barshop, 2017). A deficiency of BCKAD results in an accumulation of the three BCAAs and their metabolites.

The neurotoxicity of MSUD is secondary to the accumulation of the ketoacid of leucine, 2-oxoisocaproic acid, in the plasma and organs. Leucine intoxication impairs the volume-regulating mechanisms in the brain, liver, muscle, and pancreatic cells. A fall in serum sodium precipitates a redistribution of water in the intracellular spaces of the brain, causing cerebral edema. The brains of newborns with MSUD exhibit severe cytotoxic edema with involvement of myelinated white matter on MRI (Kilicarslan, Alkan, Demirkol, Toprak, & Sharifov, 2012).

Clinical Manifestations. The neonate with classical MSUD is usually born at term after an uncomplicated pregnancy and delivery. A short symptom-free interval occurs after birth. During this time, the usual postnatal endogenous protein catabolism causes a progressive rise in BCAA levels, with concomitant metabolic acidosis.

By about 48 hours of age, the untreated infant begins to show signs of the disorder. The earliest and most specific sign is the

Box 9.3

UNUSUAL ODORS ASSOCIATED WITH EMS

Disorder	Odor
Maple syrup urine disease	Maple syrup—burnt sugar
Tyrosinemia type I	Cabbage or rancid butter
Multiple acyl-CoA dehydrogenase deficiency	Sweaty socks—rancid cheese
Phenylketonuria	Mousy—musty
Propionic acidemia	Cat urine
Isovaleric acidemia	Sweaty socks—rancid cheese
Ketoaciduria	Fruity
3-Methylglutaconic aciduria	Tomcat urine
Trimethylaminuria	Fish

unique maple syrup odor of the cerumen. Other early signs and symptoms of MSUD are feeding difficulties, irritability, lethargy, and dystonia. Over the ensuing hours, neurologic deterioration predominates, as drowsiness and lethargy progress to coma. Periods of lethargy and hypotonia alternate with muscular rigidity, hypertonia, and seizures. Opisthotonic posturing is a characteristic feature of classic MSUD (Hoffmann et al., 2017).

Diagnosis. Early diagnosis and management are essential to prevent permanent brain damage. MSUD is diagnosed by plasma amino acid assay. An elevated leucine level and a high leucine-to-alanine ratio are diagnostic of MSUD. A dinitrophenylhydrazine (DNPH) test of the urine, which screens for the presence of alpha-ketoacids, will be positive. Urine should also be tested for ketones, which are typically present. Ketonuria is never normal in the neonate and should always suggest the possibility of an EM. Urinary organic acid analysis should also be performed.

By the time of diagnosis on clinical grounds, many infants with MSUD are severely encephalopathic and require emergency therapy to lower the BCAA levels. Newborn screening by MS/MS allows for detection of elevated BCAA concentrations in blood in patients with classic MSUD before the onset of severe encephalopathy. All states include MSUD on their newborn screening panels. Unfortunately, these specimens are often collected after 24 hours of age, and results are not reported until infants are 6 to 10 days of age. An infant with classic MSUD would already be seriously ill by that time.

Management. The aims of treatment of MSUD are to rapidly lower the plasma leucine level and achieve stable, long-term metabolic control with a carefully monitored low-BCAA diet. Hemodialysis, hemofiltration, or ECMO are used to remove toxins. High-energy enteral or parenteral nutrition, with close monitoring of BCAA levels, is the dietary therapy used in the newborn period to augment toxin removal. Even after the infant is in good metabolic control, however, common infections and injuries can rapidly induce biochemical disturbances requiring prompt changes in management to prevent a metabolic crisis (Cederbaum, 2018).

Isovaleric Acidemia

Isovaleric acidemia (IVA) is a disorder of leucine metabolism caused by mutations in the gene encoding the enzyme isovaleryl-CoA dehydrogenase, mapped to chromosome 15. IVA has an incidence of about 1 in 67,000 live births (Ensenauer et al., 2011). The disorder has both an acute and chronic form; the acute form manifests in the neonatal period as catastrophic disease.

Pathophysiology. Isovaleryl-CoA dehydrogenase catalyzes the third step in the catabolism of the BCAA leucine in the inner mitochondrial matrix (Grünert et al., 2012). A deficiency of isovaleryl-CoA dehydrogenase leads to accumulations of highly toxic free isovaleric acid, 3-hydroxyvaleric acid, and N-isovalerylglycine. Excess organic acids in the bloodstream inhibit gluconeogenesis and ureagenesis, predisposing the infant to both hypoglycemia and hyperammonemia, and causing fulminant metabolic acidosis (Grünert et al., 2012). Hypoglycemia stimulates the release of free fatty acids, which are transported into the mitochondria where they are oxidized to produce ketones, the source of ketosis in infants with IVA, and other organic acidemias. These organic acids also arrest maturation of hematopoietic precursors, leading to leukopenia and thrombocytopenia (Hoffmann et al., 2017; Wilcken, 2010).

Clinical Manifestations. Infants with IVA become extremely ill in the first week of life. Early symptoms are poor feeding, vomiting, lethargy, and hypothermia. Clinical evidence of dehydration is often present. **Emergency Alert: Untreated infants progress to coma, and less than half survive the initial metabolic crisis.** IVA can be recognized by the unpleasant "sweaty feet" or "rancid cheese" odor of body fluids. Hepatomegaly is present in some infants.

Diagnosis. The diagnosis of IVA is based on the presence of isovalerylglycine and its metabolites in urine, and of isovalerylcarnitine in plasma. Plasma organic acid analysis also reveals markedly elevated N-isovalerylglycine and 3-hydroxyvaleric acid. A secondary carnitine deficiency can develop. Both ketosis and metabolic acidosis, with an elevated anion gap, are present. Secondary derangements include hyperammonemia, thrombocytopenia, neutropenia, and anemia. IVA can be detected by MS/MS using filter-paper blood-spot samples and is included on the recommended uniform newborn screening panel (HHS, 2018).

Management. Infants who are extremely ill as a result of accumulation of isovaleric acid will need exogenous toxin removal with hemodialysis, hemofiltration, or ECMO (Cederbaum, 2018). Supplementation with L-glycine is also effective for IVA. Glycine promotes the formation of isovalerylglycine, which is excreted more efficiently than free isovaleric acid. L-Carnitine is given to replace lost carnitine and to provide substrate for the formation of isovalerylcarnitine, a nontoxic by-product that can be excreted in the urine (Cederbaum, 2018). If metabolic acidosis is severe, bicarbonate therapy is indicated. **Quality and Safety: Adequate fluids are mandatory to promote excretion of isovaleric acid because the primary route of elimination is the kidney.** Urine output must be carefully monitored. Initially, until the diagnosis is confirmed, protein is removed from the diet and a high-energy intake of glucose and intralipid is administered. Nutritional support is subsequently provided in the form of leucine-free amino acid mixtures followed

by a reduced leucine diet. It is important to reintroduce a balanced nutritional intake, including protein, as soon as possible to promote an anabolic state in these infants.

Propionic Acidemia

Propionic acidemia (PA) is a severe autosomal recessive disorder caused by mutations in the genes that encode the two nonidentical subunits (alpha and beta) of the propionyl-CoA carboxylase enzyme. Its estimated incidence is less than 1 in 100,000 births.

Pathophysiology. Propionyl-CoA carboxylase is involved in the metabolism of BCAA, odd-chain fatty acids, and cholesterol (Daniotti et al., 2011). Propionyl-CoA carboxylase is necessary for the synthesis of nicotinamide adenine dinucleotide, the main substrate of the mitochondrial respiratory chain (Romano et al., 2010). Propionate is a product of catabolism of amino acids (isoleucine, valine, threonine, and methionine), oxidation of odd-chain fatty acids, and gut bacterial activity. A deficiency of propionyl-CoA carboxylase results in an accumulation of toxic organic acid metabolites in the mitochondria causing severe ketoacidosis (see also Isovaleric Acidemia).

Clinical Manifestations. The clinical features of PA typically manifest shortly after birth, beginning with poor feeding, vomiting, lethargy, and hypotonia (Chapman et al., 2012). Ketonuria and metabolic acidosis develop in most infants, and severe intracellular dehydration may develop. Seizures often follow. Hepatomegaly may stem from steatosis. Infants with PA are susceptible to bacterial infections as a result of neutropenia and thrombocytopenia. The odor imparted to body fluids by propionic acid has been likened to "cat urine." Cardiomyopathy of uncertain pathogenesis is associated with PA (Romano et al., 2010) and may be associated with rapid deterioration and death in infants with this disorder. Magnetic resonance spectroscopy confirms compromised aerobic metabolism within brain tissue during acute metabolic decompensation (Davison et al., 2011). Neurologic sequelae of PA include encephalopathy, hypotonia, seizures, extrapyramidal symptoms, optic nerve atrophy, and stroke-like episodes (Johnson, Le, & Palacios, 2009).

Diagnosis. In most cases, there is a marked elevation of free propionate in the blood and urine. However, these findings are occasionally absent, and in those cases, significant elevations of other propionate metabolites, such as propionyl-carnitine, beta-hydroxypropionate, and methylcitrate, help to establish the diagnosis. However, propionyl-carnitine is not specific for PA; it can be elevated in MMA and disorders of vitamin B_{12} transport and synthesis (Chapman et al., 2012). Plasma glycine is also increased, but plasma carnitine is low. The diagnosis of PA can be confirmed either with analysis of enzyme activity in leukocytes or fibroblasts, or with specific mutation analysis. PA can be detected by MS/MS using filter-paper blood-spot samples and is included on the recommended uniform newborn screening panel (HHS, 2018), allowing presymptomatic diagnosis for some infants (Chapman et al., 2012).

Management. PA is unique in that the urinary excretion of the toxin, propionic acid, is negligible, and no alternate route can adequately remove the toxin from affected newborns. Emergency treatment to remove toxins using hemodialysis or hemofiltration is imperative. Initially, protein intake is stopped and a high-calorie intake of glucose and intralipid or nonprotein formula is substituted to suppress catabolism. Protein is reintroduced in small quantities after a few days of protein restriction. Secondary hyperammonemia may respond to administration of N-carbamylglutamate (Ah Mew et al., 2010; Kasapkara et al., 2011), sodium benzoate, sodium phenylacetate, or a combined preparation to provide an alternate route for excretion of nitrogen. In some cases, dramatic response to N-carbamylglutamate has obviated the need for hemodialysis (Fillippi et al., 2010). Blood ammonia levels should be followed closely. Carnitine supplementation, to prevent carnitine deficiency and to augment excretion of propionate, has also been used in the early management of infants with PA. In addition, because propionyl-CoA is a biotin-containing enzyme, biotin and cobalamin are given to evaluate for a vitamin-responsive disorder.

Antimicrobial therapy with oral broad-spectrum antibiotics, such as metronidazole or neomycin, inhibits anaerobic colonic flora, thereby suppressing propionate production in the gut. Infants with PA are immune-compromised and easily susceptible to infection; therefore, strict measures to avoid exposure to microbes must be observed. Laboratory indicators of infection must be monitored closely. Infants with PA should also be assessed for evidence of cardiac failure secondary to cardiomyopathy. Long-term dietary management consists of a low-protein, high-energy diet centered on the proportion of valine, a direct precursor to propionyl-CoA. Discharge teaching should include the importance of seeking medical attention immediately for any sign of illness or infection, because even a minor illness can lead to rapid deterioration in an infant with PA.

Methylmalonic Acidemia

MMA is really a group of disorders representing inherited deficiencies of the activity of methylmalonyl-CoA mutase, a vitamin B_{12}–dependent enzyme. MMA is one of the more common organic acidemias, occurring in about 1 in 25,000 to 48,000 infants. About half of the mutations causing MMA are in the genes encoding this enzyme; other mutations can occur in genes required for provision of cobalamin cofactors. In the most severe form of MMA, enzyme activity is completely absent.

Pathophysiology. Methylmalonyl-CoA mutase is normally responsible for the conversion of methylmalonyl-CoA to succinyl-CoA, a Krebs cycle intermediate. The lack of methylmalonyl-CoA mutase activity results in an intracellular accumulation of methylmalonic acid, impairing mitochondrial oxidative metabolism. A secondary inhibition of propionyl-CoA results in an accumulation of propionic acid and its metabolites. These compounds have inhibitory effects on many intermediary metabolic pathways, leading to hypoglycemia, hyperammonemia, and hyperglycinemia. Conjugation with carnitine results in a relative carnitine deficiency.

Clinical Manifestations. Most infants with MMA begin showing symptoms before the end of the first week of life. Lethargy, hypotonia, and vomiting with signs of dehydration are followed by respiratory distress, acute encephalopathy, and eventual coma. Untreated infants develop hypoglycemia, hyperammonemia, anion gap metabolic acidosis, and ketosis. MMA is similar to PA in that many infants become neutropenic and thrombocytopenic.

Diagnosis. Plasma methylmalonic acid and propionyl-carnitine are increased in MMA. The presence of C4-dicarboxylic acylcarnitine distinguishes MMA from PA. Urine organic acid analysis demonstrates greatly increased methylmalonic acid and its precursors, methylcitric acid and beta-hydroxypropionate. MMA is detected by MS/MS in states that have adopted the recommended uniform newborn screening panel (HHS, 2018). Among the many other nonspecific laboratory findings in MMA are metabolic acidosis, hyperammonemia, hyperglycinemia, leukopenia, anemia,

thrombocytopenia, and ketonuria. Molecular genetic testing is available for prenatal diagnosis.

Management. Infants who are severely moribund and those with extreme hyperammonemia (>600 µmol/L) are likely to have very high levels of toxic organic acids that must be removed expeditiously with hemodialysis or hemofiltration. Severe hyperammonemia can also be treated with N-carbamylglutamate (Tuchman et al., 2008), sodium benzoate, or sodium phenylacetate or a combined preparation to provide an alternate pathway for nitrogen removal. The acute metabolic crisis of MMA is further managed with protein restriction and administration of intravenous glucose and intralipid. Adequate fluid intake will enhance the elimination of methylmalonic acid, which is relatively efficiently removed from the body by the kidneys. Blood gases should be monitored to evaluate the degree of metabolic acidosis, and sodium bicarbonate may be required to control severe metabolic acidosis. In the event that the infant has a cofactor-responsive disease, pharmacologic doses of vitamin B_{12} are given. Because excess propionate is also a problem in MMA, broad-spectrum antibiotics are given to inhibit anaerobic flora and reduce intestinal propionate production. Supplemental carnitine is used to replace carnitine depletion and promote urinary propionylcarnitine elimination.

Like infants with PA, those with MMA are at high risk for infection owing to compromised immunity reflected by neutropenia and thrombocytopenia. Close monitoring of clinical and laboratory indicators of infection is warranted. These infants must also be monitored for evidence of cardiac failure related to cardiomyopathy. The discharge planning needs of infants with MMA are similar to those of infants with PA. Parents or other caretakers must be aware that even a minor illness or infection in their baby with MMA can represent a potential metabolic crisis and requires prompt medical attention.

FATTY ACID OXIDATION DISORDERS

FAODs are a subset of organic acid disorders that are among the most common of the known inherited disorders of metabolism. The population frequency of FAODs is estimated to be 1 in 8,000 to 16,000, although a number of neonates die before the diagnosis is made. An FAOD can be caused by a deficiency of any of the enzymes involved in cellular uptake, transport, and mitochondrial oxidation of fatty acids. To date, more than 20 defects and their gene mutations have been discovered (Rector & Ibdah, 2010). The most common is MCAD. Short, long, and very long chain forms of this enzyme deficiency also exist (SCAD, LCAD, very long chain acyl-CoA dehydrogenase [VLCAD]), as well as carnitine transporter defects, and deficiencies of the mitochondrial trifunctional protein (MTP) complex. The FAODs are considered treatable, and the prognosis for many FAODs has improved in recent years (Wilcken, 2010).

Pathophysiology

The fatty acids are the largest source of energy in the body and are the preferred fuels of the liver, heart, and skeletal muscles. Neonatal brown fat uses fatty acids to sustain nonshivering thermogenesis. When glucose levels are low during long periods between feedings, glucagon secreted by the pancreas stimulates adipose cell lipase to liberate free fatty acids. These fatty acids are oxidized to provide energy through the mitochondrial beta-oxidation pathway. Fatty acid oxidation also provides the substrate for hepatic ketogenesis. Fatty acids as a source of energy are particularly critical for the neonate who has limited stores of glycogen and a high metabolic rate; thus, any perturbation in the fatty acid oxidation pathway can rapidly lead to metabolic decompensation.

Fatty Acid Oxidation. Three subsystems are required for the production of energy in the normal fat oxidation process (Figure 9.3): (1) the carnitine cycle, (2) the mitochondrial inner membrane system, and (3) the mitochondrial matrix system (Vockley, Longo, Andresen, & Bennett, 2017). In the first step, L-carnitine and fatty acids are taken up by the cell, and fatty acids are conjugated to fatty acyl-CoAs in the cytoplasm by enzymes of the outer mitochondrial membrane. Medium- and short-chain fatty acids can penetrate the inner mitochondrial membrane for beta-oxidation, but longer chain fatty acids of dietary fat (those with carbon lengths of 14–20) must be actively transported into the matrix via the carnitine cycle. Activated acyl-CoAs are converted to carnitine esters by carnitine palmitoyltransferase I (CPT1), transported across the mitochondrial membrane by carnitine-acylcarnitine translocase, and reactivated by carnitine palmitoyltransferase II (CPT2).

Within the mitochondrion, long-chain acyl-CoAs are degraded by enzymes in the inner membrane system in a recurring cyclic sequence of four reactions (Vockley et al., 2017). These are catalyzed by VLCAD and the MTP complex encompassing the three enzymes required for a single cycle of beta-oxidation: enoyl-CoA hydratase, L to 3-hydroxy acyl-CoA dehydrogenase (LCHAD), and thiolase. In each full cycle, the fatty acid is progressively shortened by two carbons from long to medium, and finally to short-chain acyl-CoAs. The final system, the mitochondrial matrix, oxidizes shorter chain length fatty acids resulting from the enzymatic steps in the inner membrane system. L-Carnitine is not required for the latter process. The result of the beta-oxidation system is generation of acetyl-CoA, used by the liver to produce ketone bodies and as a major source of cellular ATP.

Defective Fatty Acid Oxidation. Inborn errors of fatty acid oxidation result in a buildup of toxic metabolites both proximal and distal to the block, and an insufficient yield of substrate for energy production. A deficiency of any of the enzymes required for fatty acid transport or metabolism can result in a failure of fatty acid oxidation. The primary physiologic consequence is inadequate ATP and ketone body generation, and a failure of energy production. This becomes apparent during periods of increased energy demand, such as a prolonged period of fasting, fever, or other illness. Under normal circumstances, when glycogen stores are depleted in the newborn, free fatty acids are released as a source of energy. However, the neonate with a FAOD is unable to use fatty acids for fuel and rapidly becomes hypoglycemic. As a result of hypoketogenesis, the brain is without an alternate fuel source. Without early treatment, neurologic morbidity and mortality are high. A second consequence of FAODs is the accumulation of fatty acids and their derivatives, which can have toxic effects. When their oxidation is blocked, fatty acids are stored in the cytosol as triglycerides, resulting in muscular, hepatic, and cardiac lipidoses. Skeletal muscle tissue begins to break down (rhabdomyolysis), causing a skeletal myopathy characterized by muscle weakness. In defects downstream from CPT1 in the carnitine cycle, the acylcarnitine that accumulates has detergent-like properties that may disrupt the integrity of muscle membranes. In the heart muscle, accumulated long-chain fatty acyl-CoAs can produce electrophysiologic abnormalities, including arrhythmias and cardiac arrest.

Clinical Manifestations

Affected neonates are almost always born at term. A fasting stress sufficient to reveal the disorder can result with early breastfeeding, especially in infants who do not nurse well (Jameson & Walter,

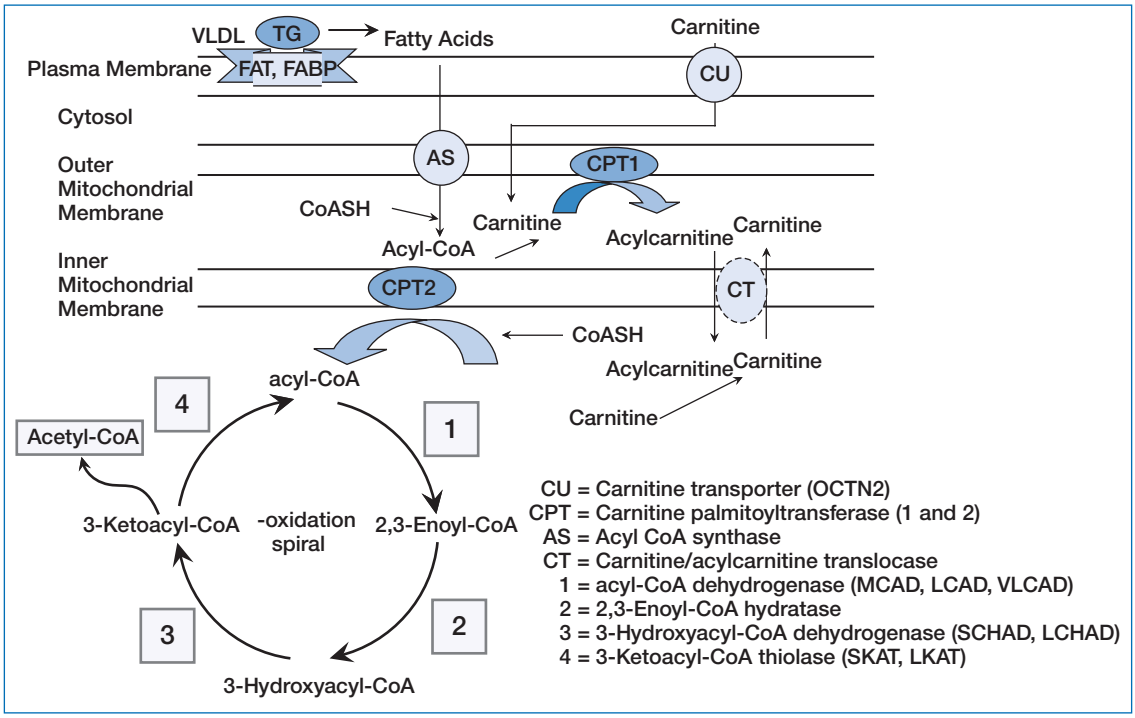

FIGURE 9.3 The mitochondrial fatty acid oxidation pathway. This schematic representation shows the uptake of fatty acids and carnitine into the cell, transfer of fatty acid from the cytosol into mitochondria, and the fatty acid beta-oxidation spiral.

LCAD, long chain acyl-CoA dehydrogenase; LCHAD, long-chain 3-Hydroxyacyl-CoA dehydrogenase; LKAT, long-chain 3-Ketoacyl-CoA thiolase; MCAD, medium chain acyl-CoA dehydrogenase deficiency; OCTN2, organic cation/carnitine transporter 2; SCAD, short chain acyl-CoA dehydrogenase; SCHAD, short-chain 3-Hydroxyacyl-CoA dehydrogenase; SKAT, 3-Ketoacyl-CoA thiolase; VLCAD, very long chain acyl-CoA dehydrogenase.

Source: Adapted from Shekhawat, P., Bennett, M. J., Sadovsky, Y., Nelson, D. M., Rakheja, D., & Strauss, A. W. (2003). Human placenta metabolizes fatty acids: Implications for fetal acid oxidation disorders and maternal liver diseases. *American Journal of Physiology, Endocrinology & Metabolism, 284*, E1098–E1105. doi:10.1152/ajpendo.00481.2002

2010). Mitochondrial FAODs in the neonate present with three clinical phenotypes that, depending on the disorder, can be seen individually or in combination: hypoketotic hypoglycemia, cardiomyopathy, and skeletal myopathy (Rector & Ibdah, 2010). Neonates with MCAD, the most common of the FAODs, usually present with glucose instability, but there have been reports of acute life-threatening episodes and even sudden death (Rector & Ibdah, 2010).

Neonates with VLCAD are similarly intolerant to fasting and develop hypoglycemia without ketosis. Moreover, VLCAD can be associated with evidence of cardiomyopathy, including cardiomegaly, ventricular arrhythmias, or unexplained cardiac arrest. Other physical findings that have been reported in neonates with disorders of fatty acid oxidation include hypotonia, seizures, irritability or lethargy (mimicking acute encephalopathy), hepatomegaly, and associated congenital malformations such as cystic renal dysplasia.

Diagnosis

A FAOD must be considered in any infant with an unexplained nonketotic hypoglycemia, hepatic dysfunction, isolated arrhythmia, or cardiomegaly. The initial screen for FAOD includes urine organic acid analysis, as well as plasma and urine free and total carnitine, collected during a period of acute decompensation. A strong clue to a FAOD is urinary excretion of dicarboxylic acids, compounds not normally found in the urine (Rector & Ibdah, 2010). Plasma carnitine levels will be markedly reduced.

To reach a specific diagnosis of mitochondrial fat oxidation, a plasma acylcarnitine profile must be obtained (Rector & Ibdah, 2010). Using whole blood samples on filter paper and MS/MS, the acylcarnitine intermediates formed as a result of the enzymatic block somewhere in the fat oxidation cycle can be quantified. A plasma acylcarnitine profile reveals accumulation of acyl-CoA conjugates proximal to the defect. When MS/MS screening is not available, the most useful indirect laboratory tests in neonates with suspected FAODs are glucose, electrolytes, BUN, creatinine, lactate, ammonia, transaminases, and creatine kinase. Elevated creatine kinase and myoglobinuria reflect rhabdomyolysis. Plasma carnitine levels are markedly reduced, except in CPT1 deficiency (Vockley et al., 2017). Additional laboratory results may show hyperammonemia, metabolic acidosis, and increased uric acid and transaminases. A liver biopsy performed during the acute phase usually reveals microvesicular and macrovesicular fatty infiltration.

Family and perinatal history can be particularly important to the diagnosis of a FAOD. Many infants diagnosed with a FAOD have a history of a sibling who died of SIDS. In addition, an association has been found between acute fatty liver of pregnancy (AFLP) or HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome in the mother and fetal deficiency of long-chain 3-hydroxyacyl coenzyme A dehydrogenase (LCHAD), one of the enzymes in the MTP complex. When a woman is carrying an affected fetus, the placenta and fetus are unable to oxidize fatty acids, leading to transfer of accumulated fatty acid intermediates to the maternal circulation. For unclear reasons, in some women these fatty acids overwhelm the maternal liver and contribute to HELLP syndrome and maternal hepatic fat deposition (AFLP).

The newborn infants of women with AFLP or mothers who are known carriers for FAODs should be evaluated immediately after birth with blood-spot acylcarnitine profiles, and treated as if they have a FAOD until test results are known.

Neonatal Screening and Confirmatory Testing for FAOD. The key to preventing the morbidity and mortality associated with FAOD is through presymptomatic diagnosis, allowing early

treatment and avoidance of metabolic crisis. Neonatal screening for FAODs by MS/MS analyzes acylcarnitines from dried blood spots and can identify 22 different abnormalities. However, an abnormal acylcarnitine profile can represent more than one FAOD, so more specific testing is required. Using cultured skin fibroblasts (or amniocytes) that have been incubated with deuterium-labeled fatty acid precursors and excess L-carnitine, MS/MS can rapidly detect any enzyme defect from translocase through SCAD. This method is possible because the enzymes of fatty acid oxidation are also expressed in the skin and other cells. Mutational analysis, if available, can also provide a definitive diagnosis (Vockley et al., 2017).

Management

The primary goal is to provide nutrition that will control endogenous lipolysis and prevent tissue catabolism. This involves a high-carbohydrate, low-fat diet. The newborn should feed every 3 to 4 hours, with close monitoring of blood sugar level. Breastfeeding mothers should receive lactation assistance to ensure successful breastfeeding with evidence of milk transfer. If hypoglycemia persists or the infant is unable to tolerate enteral feeding, glucose should be administered intravenously. Closely monitor for cardiac conduction disturbances.

The nurse is in a key position to prevent stressors, such as hypothermia or pain, that could precipitate a metabolic crisis, and to assess the infant for signs of intercurrent illness that might require additional therapy. Discharge teaching should emphasize the need to avoid prolonged periods of fasting and to seek medical attention if the infant shows signs of illness (fever, vomiting, diarrhea, refusal to eat, lethargy, or any other change in normal behavior). A consult should be made with a neonatal nutritionist or dietary specialist to arrange teaching for the family about the infant's postdischarge dietary regimen. The infant's diet will continue to be high in carbohydrate and restricted in fat. Supplementation with l-carnitine has not been shown to be beneficial (Spiekerkoetter et al., 2010).

Multiple Acyl-CoA Dehydrogenase Deficiency (Glutaric Aciduria Type II)

Pathophysiology. Multiple acyl-CoA dehydrogenase deficiency (MADD), formerly known as glutaric aciduria type II, is a disorder caused by a defective electron transfer flavoprotein (ETF) or electron transfer flavoprotein dehydrogenase (ETF-QO). MADD impairs both fatty acid oxidation and oxidation of branched amino acids lysine and glutaric acid. The heart, liver, and kidneys become infiltrated with fat.

Clinical Manifestations. Two different neonatal presentations have been described for MADD; both involve overwhelming illness with rapid progression to coma and death (Vockley et al., 2017). One presentation is a neonate, often preterm, with dysmorphic facial features, polycystic kidneys, and hepatomegaly. Within the first 24 to 48 hours of life, the infant develops hypotonia, metabolic acidosis, severe nonketotic hypoglycemia, and a distinctive "sweaty feet" odor of body fluids. The alternate neonatal presentation is the infant without congenital anomalies, but with similar symptoms and metabolic aberrations. Neither group lives longer than a few weeks; the few babies who survive generally succumb at a few months of age to cardiac failure.

Diagnosis. MS/MS rapidly detects elevated acylcarnitines (C4, C5, C8, C10, and C16). Quantitative urine organic acid analysis usually reveals a pattern of elevated organic acids: lactic, glutaric, 2-hydroxyglutaric, ethylmalonic, adipic, suberic, sebacic, and other acids, some in very high amounts. The same organic acids are increased in the plasma. Volatile acid (isovaleric, acetic, isobutyric, propionic, butyric) concentrations in plasma are excessive, accounting for the characteristic odor associated with the disorder. Plasma carnitine may be low. Mutations have been identified in the genes for flavoproteins ETF and ETF-QO.

Management. There is no effective treatment other than supportive care (fluids, glucose, sodium bicarbonate) for the rapid-onset, severe neonatal presentation. For the rare infant who survives the initial crisis, management involves frequent feedings with avoidance of fasting, and a diet low in fat and protein and high in carbohydrates. Some patients also respond to riboflavin.

CONGENITAL LACTIC ACIDOSES

The congenital lactic acidoses (also called primary lactic acidoses) are a group of disorders of lactate metabolism caused by defects in the mitochondrial respiratory or electron transport chain, the tricarboxylic acid (Krebs) cycle, or in pyruvate metabolism.

Lactic acid is the major end product of anaerobic glycolysis, accumulating when production of pyruvate exceeds utilization. The brain's dependence on oxidative metabolism makes it particularly susceptible to damage in disorders of oxidation that lead to lactic acidosis.

Pyruvate Dehydrogenase Deficiency

PDH complex disorders are the most common inborn errors of pyruvate metabolism. Most cases of PDH are caused by mutations in the X-linked *PDHA1* gene, which encodes the E1 alpha subunit of the PDH enzyme complex (Brown, 2012).

Pathophysiology. PDH complex efficiently and irreversibly converts pyruvate, a product of glucose metabolism, to acetyl-CoA. Acetyl-CoA is one of two essential substrates needed to generate citrate for the energy-producing tricarboxylic acid cycle (also called the citric acid cycle or Krebs cycle). Thus, PDH provides the link between glycolysis and the tricarboxylic acid cycle. PDH complex activity is regulated primarily by reversible phosphorylation (inactivation) of the enzyme's E1 alpha subunit. A deficiency in the PDH complex limits the production of acetyl-CoA, and in turn the production of citrate, blocking the tricarboxylic acid cycle and creating an energy deficit. Persistent glycolysis without pyruvate oxidation leads to the accumulation of lactate because excess pyruvate is reduced to lactate in the cytoplasm. Tissues with high-energy requirements, such as those of CNS, are vulnerable to injury when cellular energy production is impaired.

Clinical Manifestations. The nonspecific early signs and symptoms of PDH deficiency develop soon after birth and are similar to those of other metabolic disorders. Poor feeding, lethargy, and tachypnea are followed by progressive neurologic deterioration, apnea, seizures, and coma. Fulminant lactic acidosis is present in infants with profound deficiencies of the PDH complex, and these patients often die early in the neonatal period. Infants with severe disease may have prenatal onset leading to structural brain abnormalities including microcephaly. MRI may show ventricular dilatation, cerebral atrophy, hydrancephaly, partial or complete absence of the corpus callosum, and periventricular leukomalacia (Sharma, Sharrard, Connolly, & Mordekar, 2012). Patients with PDH complex deficiency can also present with Leigh syndrome.

Diagnosis. Lactic acidosis is an important biochemical marker for mitochondrial dysfunction. Hyperlactatemia, with an elevated

lactate–pyruvate ratio, is predictive of early demise (Patel, O'Brien, Subramony, Shuster, & Stacpoole, 2012). Lactate and pyruvate are also often elevated in the CSF of babies with this disorder. Plasma and urine amino acid analysis reveal hyperalaninemia. A definitive diagnosis of enzyme activity requires testing of leukocytes, fibroblasts, or tissue samples, or DNA analysis.

Collaborative Management. No effective treatment has been found to date for any of the PDH complex defects that manifest in the neonatal period. Therapies include alternate dietary regimens or vitamins such as thiamine that might stimulate residual enzyme activity or circumvent the enzyme defect. Because infants with PDH complex deficiency oxidize carbohydrates poorly, a ketogenic (high-fat, low-carbohydrate) diet has been used to provide an alternate energy source for acetyl-CoA production (Patel et al., 2012). These diets may reduce hyperlactatemia and improve short-term neuromuscular function in infants with PDH complex deficiency. Cofactor supplementation with thiamine, carnitine, and lipoic acid is another facet of the management of these infants.

Recently, dichloroacetate (DCA) has been used to treat PDH complex deficiency. DCA is believed to activate PDH complex activity by inhibiting PDH kinase. PDH complex is thereby "locked" in its unphosphorylated, catalytically active form (Patel et al., 2012).

Pyruvate Carboxylase Deficiency

PCD is a disorder of energy metabolism that exists in three different forms. The most severe of these is a neonatal-onset form known as type B, a disorder with a high mortality rate. All forms of PCD have a frequency of about 1 in 250,000 live births and are recessively inherited.

Pathophysiology. Pyruvate carboxylase is a biotin-containing mitochondrial enzyme responsible for the ATP-dependent carboxylation of pyruvate. This enzyme also catalyzes the conversion of pyruvate to oxaloacetate, an essential substrate in gluconeogenesis, glycogen synthesis, lipogenesis, and other metabolic pathways (Marin-Valencia, Roe, & Pascual, 2010). The absence of pyruvate carboxylase activity results in malfunction of the citric acid cycle and gluconeogenesis, thereby disrupting energy metabolism in the brain. A deficiency of aspartic acid, derived from oxaloacetate, disrupts the urea cycle as well, leading to a simultaneous failure of nitrogen excretion.

Clinical Manifestations. In PCD with neonatal onset, the earliest signs and symptoms begin at 72 hours of life and include severe truncal hypotonia and tachypnea associated with profound metabolic acidosis. Seizures, abnormal eye movements, and coma can occur. Hyperammonemia, hypoglycemia, ketosis, and ketonuria are frequent findings. Renal tubular acidosis can also accompany PCD.

Diagnosis. The diagnosis of PCD is based on the measurement of urinary organic acids and blood acylcarnitine profile. In type B PCD, the lactate–pyruvate ratio may be high (≥25). Plasma citrulline and lysine are elevated along with the ammonia level. Serum transaminases may also be elevated. The diagnosis can be confirmed by enzyme analysis of hepatic cells or leukocytes.

Management. PCD is a progressive disorder with no specific therapy. Some infants have biotin-responsive disease, so pharmacologic doses of biotin are administered and the response is evaluated. Therapeutic options that involve replenishment of citric acid cycle intermediates to interrupt the hyperactive catabolic cascade associated with the disorder and enhance ATP production are being explored (Marin-Valencia et al., 2010).

DISORDERS OF CARBOHYDRATE METABOLISM

Galactosemia

Galactosemia is an inherited disorder of carbohydrate metabolism caused by a deficiency in one of the three enzymes of the galactose metabolic pathway: galactose-1-phosphate uridyl transferase (GALT), galactokinase (GALK), or UDP-galactose-4-epimerase (GALE). GALT deficiency, affecting the second step in the galactose metabolism, accounts for more than 95% of galactosemias; thus, it has become synonymous with classic galactosemia.

Galactosemia has an estimated prevalence of 1 in 40,000 to 60,000 live births (Berry, 2012). At least 24 different mutations have been identified to date in the human GALT gene, located on chromosome 9.

Pathophysiology. Infants with galactosemia are unable to metabolize the sugar galactose, derived from the disaccharide lactose, the major carbohydrate of mammalian milk. In normal galactose metabolism, galactose is first converted to galactose-1-phosphate by GALK, which is in turn converted by the GALT enzyme to uridyl diphosphate (UDP) glucose. The severe form of galactosemia features near total deficiency of GALT enzyme activity in all cells of the body. In the absence of GALT, ingestion of lactose-containing substances produces toxic levels of galactose-1-phosphate within cells. Surplus galactose is reduced to galactitol or oxidized to galactonate, metabolites that also have a direct toxic effect on the liver and other organs.

Clinical Manifestations. Most patients present in the neonatal period or in the first week or two of life. After ingestion of galactose (either cow's milk–based formula or breast milk), vomiting, diarrhea, poor weight gain, jaundice, hepatomegaly, and hypoglycemia become evident. In some infants, CNS symptoms, such as lethargy and hypotonia, predominate. Untreated infants will go on to develop cataracts secondary to the accumulation of galactitol. Sepsis, usually caused by *Escherichia coli*, is often the presenting problem, owing to low neutrophil bactericidal activity. Liver dysfunction is progressive, and many infants die during the first week of life from liver failure. In those who do survive, neurologic complications are frequent.

Two related disorders of galactose metabolism are GALK and GALE deficiencies. In GALK deficiency, galactose cannot be phosphorylated into galactose-1-phosphate. The chief clinical finding in GALK deficiency is cataract formation. In GALE deficiency, most patients are asymptomatic and have normal growth and development.

Diagnosis. A galactose assay, measuring blood galactose, RBC galactose-1-phosphate, and GALT enzyme activity, is used to diagnose classic galactosemia. GALT activity is low or absent. Galactose and galactose-1-phosphate are elevated. DNA analysis for the common mutations associated with GALT deficiency can also be done. Urine is positive for reducing substances. Galactosemia is included on all routine state newborn screening panels, allowing presymptomatic diagnosis.

Management. Galactosemia is treated by feeding a soy-based formula, containing no galactose. **Quality and Safety: Breastfeeding is not permitted. Other sources of galactose, including medications containing galactose, must also be avoided.** Dietary restriction of galactose in the newborn will reverse the hepatic, renal, brain, and immune dysfunction and reduce the accumulated galactose metabolites. Additional measures include monitoring for and treating sepsis and coagulopathy. Despite dietary treatment,

long-term neurodevelopmental outcomes have not been uniformly favorable. An important part of discharge education is dietary teaching to assist the family to maintain dietary control as the infant grows and develops and help them identify occult sources of galactose in foods and other substances.

Hereditary Fructose Intolerance

Hereditary fructose intolerance (HFI) is an inherited inability to digest fructose (fruit sugar) or its precursors (sugar, sorbitol, and brown sugar). This autosomal recessive disorder has a frequency of approximately 1 in 22,000 births.

Pathophysiology. Fructose is a naturally occurring sugar that is used as a sweetener in many foods, including many baby foods. A deficiency of activity of the enzyme fructose-L-phosphate aldolase impairs the body's ability to convert fructose-L-phosphate to glyceraldehyde and dihydroxyacetone phosphate. The outcome is an accumulation of fructose-L-phosphate in the liver, kidney, and small intestine, which inhibits glycogen breakdown and glucose synthesis and causes severe hypoglycemia following ingestion of fructose. This disorder can be life threatening to infants.

Clinical Manifestations. In the neonate, the onset of clinical symptoms follows ingestion of cow's milk formula and resembles that for galactosemia. Signs and symptoms include pallor, lethargy, poor feeding, irritability, vomiting, and hypoglycemia. Jaundice, hepatomegaly, and evidence of progressive liver disease may follow. In exclusively breastfed infants, symptoms will be delayed until the time of weaning to fruits and vegetables.

Diagnosis. The diagnosis of HFI is usually now by molecular analysis, rather than enzyme analysis or fructose tolerance testing (Merritt & Gallagher, 2018). Urine is positive for reducing substances.

Management. Management of HFI centers on removal of all sources of fructose and sucrose from the diet. All intravenous solutions and other medications must also be free of fructose, corn syrup, and sorbitol. Supportive care includes management of liver failure, kidney dysfunction, and coagulopathy, if present. The infant's parents will benefit from consultation with a dietary specialist to learn about long-term dietary management.

Fructose 1,6-Bisphosphatase Deficiency

Fructose 1,6-biphosphatase deficiency is a rare disorder of carbohydrate metabolism.

Pathophysiology. Fructose 1,6-bisphosphatase catalyzes the irreversible splitting of fructose 1,6-biphosphate into fructose 6-phosphate and inorganic phosphate. The enzyme's activity is highest in gluconeogenic tissues such as the liver and kidney. Fructose 1,6-biphosphatase deficiency is, therefore, a disorder of gluconeogenesis, resulting in glucose deprivation to the CNS.

Clinical Manifestations. In fructose 1,6-biphosphatase deficiency, hypoglycemia is precipitated by fasting, not by fructose ingestion (Merritt & Gallagher, 2018). Lactic acidosis and ketosis result from accumulating lactic, 3-hydroxybutyric, and acetoacetic acids. Hyperventilation followed by apnea may result from profound acidosis. Although the acidosis and hypoglycemia may be treated and the infant recovers from the acute attack, if the underlying disorder is not recognized, the infant can have many acute metabolic attacks and develop hepatomegaly and failure to thrive before the diagnosis is finally made.

Diagnosis. Definitive diagnosis is made by liver biopsy and assay of hepatic enzymes. Mutational analysis is available and can be used instead of biopsy.

Management. Acute management involves glucose administration with intravenous solutions and correction of acidosis with sodium bicarbonate. Frequent feedings, avoidance of fasting, and limitation of fructose and sucrose in the diet usually prevent further episodes. Dietary restriction includes the many prescription and over-the-counter medications with a syrup base containing sucrose. Stress management (e.g., during times of fever, infection, or vomiting) is critical because illness can induce a metabolic attack.

Glycogen Storage Disease

Glycogen storage disease (GSD) is a group of inherited enzyme defects that affects the glycogen synthesis and degradation cycle. Liver and muscle, having the most abundant quantities of glycogen, are usually the most severely affected tissues (Hendriksz & Gissen, 2010). More than 10 different types of GSD have been identified with a collective incidence of about 1 in 20,000 births. Glycogen storage disease type I (GSD-I, also known as von Gierke's disease), the disorder most likely to have neonatal onset, occurs in about 1 in 100,000 births and has two main subtypes (Ia, Ib). GSD-II, known as Pompe's disease, is classified as a lysosomal storage disease.

Pathophysiology. GSD-Ia, the most common subtype, is the result of a deficiency of the hepatic enzyme glucose-6-phosphatase (G6Pase), an enzyme situated in the endoplasmic reticulum of the cell. Normally, G6Pase hydrolyzes glucose-6-phosphate to glucose and phosphate. An accumulation of glycogen in the liver, kidney, and intestines results from a deficiency of G6Pase. In the normal neonate, blood glucose falls during the first postnatal hours as the neonate uses circulating glucose obtained from the mother, but then rises as endogenous glucose production begins. In the neonate with GSD-I, blood glucose continues to decline because endogenous glucose production is severely compromised. Instead, the phosphorylated intermediate compounds of glycolysis produce an excess of lactate, resulting in hyperlactacidemia. Secondary metabolic derangements typical of GSD-I include hyperuricemia and hyperlipidemia.

Clinical Manifestations. The neonate with GSD-I cannot cope with the normal postnatal drop in blood sugar. Despite a plentiful supply of glycogen, the neonate is unable to mobilize free glucose and becomes hypoglycemic. The abdomen may appear distended from birth as a result of an enlarged liver. Acute, nonspecific clinical deterioration is related to the buildup of lactic acid in the body.

Diagnosis. Definitive diagnosis of GSD-I is accomplished with molecular genetic testing. Typical laboratory findings in GSD-I include increased plasma lactate and metabolic acidosis with an increased anion gap. Ketosis and ketonuria will be found during hypoglycemia. Other routine tests that should be obtained are liver function tests, plasma uric acid, triglycerides, creatinine, coagulation studies, and complete blood count (CBC) with differential. Abdominal ultrasonography is performed to determine liver and kidney size.

Management. The goals of treatment of GSD-I are to prevent hypoglycemia and correct secondary biochemical abnormalities. Frequent feedings or continuous gastric feedings may be necessary to maintain normoglycemia and supply the brain with a steady source of glucose, even during the night. Blood glucose levels must be monitored closely. Pharmacologic therapy to address hyperuricemia and prevent the development of gout may be necessary. Very severely affected infants will require a liver transplant. Parent teaching about long-term nutritional management, prevention of hypoglycemia, and special considerations during stress or other illnesses is critically important.

PEROXISOMAL DISORDERS

Peroxisomal disorders are complex developmental and metabolic disorders caused by defects in peroxisome biosynthesis. Two of the better known disorders, Zellweger syndrome (ZS) and neonatal adrenoleukodystrophy (NALD), are now recognized as belonging to a continuous spectrum of disorders, of which ZS is the most severe. ZS has a reported incidence of about 1 in 25,000 to 50,000 births.

Pathophysiology

Peroxisomes are subcellular organelles that synthesize bile acids, cholesterol, and plasmalogens (a type of phospholipid found in myelin sheaths of nerve fibers). Peroxisomes are also critical in the beta-oxidation of very long-chain fatty acids. Peroxisomal disorders arise from either a defect in peroxisomal biosynthesis or a single peroxisomal enzyme or protein (Scott & Olpin, 2010). Individuals with peroxisome biogenesis defects such as ZS and NALD synthesize peroxisomes normally, but display defects in the import of peroxisomal enzymes into the lumen of the organelle (Merritt & Gallagher, 2018). Biochemical abnormalities include impaired degradation of peroxide, very long-chain fatty acids, pipecolic acid, and phytanic acid and impaired synthesis of plasmalogens, bile acids, cholesterol, and docosahexaenoic acid. In ZS, the extent of progressive multisystemic disease is profound; in NALD, the systemic involvement is milder, but the cerebral demyelination is more pronounced.

Clinical Manifestations

Infants with ZS present with characteristic facial dysmorphism including a high forehead, hypoplastic supraorbital ridges, flat occiput, low and broad nasal bridge, epicanthal folds, high arched palate, small nose with anteverted nares, micrognathia, large fontanelles, wide sutures, and eye abnormalities (Scott & Olpin, 2010). Typically, they have profound hypotonia, an absence of neonatal reflexes, and seizures. The disease affects every organ of the body, particularly the liver, kidney, and brain, resulting in hepatomegaly, renal cysts, white-matter abnormalities, and neuronal migration defects.

Diagnosis

Diagnosis of peroxisomal biosynthesis defects is based on indirect evidence of the defect. Initial tests for an infant with a suspected peroxisomal disorder include plasma very long-chain fatty acids, and plasmalogens in erythrocytes. Affected infants have elevated transaminases, bile acid intermediates, hypercholesterolemia, and increased iron and transferrin concentrations and are often hypoglycemic. A suspected peroxisomal disorder is confirmed by molecular studies if possible (Scott & Olpin, 2010).

Management

Currently, no successful treatment for the peroxisomal disorders is available. Management is supportive care and symptomatic therapy. The median life expectancy of ZS patients is less than 1 year. Milder forms of peroxisomal disorders may respond to dietary therapy.

LYSOSOMAL DISORDERS

The lysosomal disorders are a diverse group of inherited conditions caused by dysfunctions in enzymes (called hydrolases) responsible for the degradation of complex macromolecules, such as glycogen, sphingolipids, glycoproteins, and glycosaminoglycans (Wraith, 2010). In these disorders, a complex substrate that is normally degraded by a series of lysosomal enzymes fails to undergo degradation owing to a deficiency or malfunction of one of these enzymes (Figure 9.4). Catabolism of the substrate into soluble end products is incomplete, and insoluble intermediates that are unable to escape from the organelle accumulate within the lysosome (Wraith, 2010). More than 50 lysosomal disorders are recognized, with a collective incidence of 1 in 7,000 to 10,000 births.

Niemann–Pick Type C

Pathophysiology. Niemann–Pick type C (NP-C) is a disorder of intracellular cholesterol transport that leads to an accumulation of unesterified cholesterol in lysosomes (Thomas, Lam, & Berry, 2018). Unesterified cholesterol, sphingomyelin, phospholipids, and glycolipids are stored in excess in the liver and spleen, and glycolipids are increased in the brain.

Clinical Manifestations. Neonatal-onset NP-C is characterized by conjugated hyperbilirubinemia, ascites, hepatosplenomegaly, and hypotonia (Thomas et al., 2018). Hydrops fetalis is a rare presentation. Respiratory failure can occur owing to lipid infiltration of the lungs (Wraith, 2010).

Diagnosis. The diagnosis of NP-C requires specialized testing that must be coordinated with a metabolic laboratory. In general, the diagnosis is made on the basis of filipin staining of cultured fibroblasts and cholesterol esterification studies (Wraith, 2010). Filipin is a fluorescent probe that detects unesterified cholesterol. Biliary atresia and congenital viral infection are the chief differential diagnoses.

Management. There is no definitive or consistently effective therapy for NP-C to date. Splenectomy is sometimes necessary if anemia and thrombocytopenia are severe. Liver transplantation corrects the hepatic dysfunction but not the neurodegenerative disease.

Gaucher's Disease

Pathophysiology. Gaucher's disease, the most common of the lysosomal storage diseases, is an inborn error of glycosphingolipid metabolism caused by the deficient activity of the lysosomal

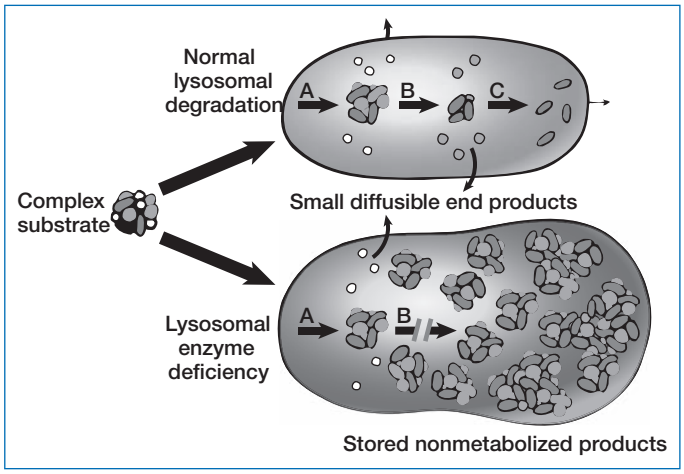

FIGURE 9.4 The pathogenesis of lysosomal storage diseases. A complex substrate is normally degraded by lysosomal enzymes A, B, and C into soluble end products. If these enzymes are deficient, catabolism is incomplete and nonmetabolized products accumulate in the lysosomes.

Source: From Kumar, V., Abbas, A. K., Fausto, N., & Aster, J. (Eds.). (2009). *Robbins and Cotran: Pathologic basis of disease* (8th ed.). Philadelphia, PA: Elsevier.

enzyme acid beta-glucosidase. Widespread accumulation of glucosylceramide-laden macrophages results from the enzyme deficiency. These accumulated compounds are toxic to various tissues in the body. There are three types of Gaucher's disease. Type I is the most common (95%). A subset of type II, a neuronopathic form of Gaucher's disease, is the only one with neonatal onset.

Clinical Manifestations. Neonates with type II Gaucher's disease can present with congenital ichthyosis or a collodion membrane (hyperkeratotic scale), hepatosplenomegaly, and/or nonimmune hydrops fetalis, hypertonicity, seizures, and other evidence of neurologic deterioration.

Diagnosis. Diagnosis is made by analysis of acid beta-glucosidase activity in white blood cells or DNA analysis. Characteristic Gaucher cells (large, lipid-laden macrophages with foamy cytoplasm) can be seen in a bone marrow aspirate.

Management. Enzyme replacement therapy for Gaucher's disease is available, but has not been very effective for patients with type II disease. Splenectomy may be necessary to manage severe anemia and thrombocytopenia. Death from respiratory insufficiency or severe neurologic disease usually occurs shortly after birth or within the first year of life.

GM1 Gangliosidosis

Pathophysiology. Gangliosides are normal components of cell membranes, particularly neurons. GM1 gangliosidosis is a devastating lysosomal storage disease caused by a deficiency of the enzyme acid beta-galactosidase, resulting in a generalized accumulation of GM1 gangliosides, oligosaccharides, and the mucopolysaccharide keratan sulfate in both the brain and viscera.

Clinical Manifestations. Affected infants may have coarse facial features known as a "Hurler phenotype" (frontal bossing, depressed nasal bridge, maxillary hyperplasia, large ears, wide upper lip, macroglossia, and gingival hyperplasia), hirsutism of forehead and neck, macular cherry-red spots, and corneal clouding (Figure 9.5). The dysmorphic features might not be obvious in the neonate (Thomas et al., 2018). Facial edema, pitting edema of the extremities, or ascites may also be apparent, and the neonate may present with hydrops fetalis and placental evidence of vacuolated cells. Neurologic examination reveals hypotonia and hypoactivity. The liver and spleen are both enlarged upon palpation.

FIGURE 9.5 The "Hurler phenotype" seen in some neonates with lysosomal storage disorders.

Source: From Wraith, J. E. (2002). Lysosomal disorders. *Seminars in Neonatology, 7,* 81. doi:10.1053/siny.2001.0088

Diagnosis. Diagnosis is made by demonstrating lack of beta-galactosidase activity in white blood cells. Galactose-containing oligosaccharides can also be measured in the urine.

Management. Currently, there is no effective therapy for infants with GM1 gangliosidosis. Enzyme and gene therapies are being studied as potential treatments for this lethal disorder.

Mucopolysaccharidoses

Pathophysiology. The mucopolysaccharidoses (MPS) are a family of seven disorders caused by deficiency of lysosomal enzymes required for the stepwise degradation of glycosaminoglycans (polysaccharides that make up an important component of connective tissue). The undegraded glycosaminoglycans are stored in lysosomes, causing cell, tissue, and organ dysfunction. MPS VII, the type with the most prominent neonatal presentation, is caused by a deficiency of the enzyme beta-glucuronidase.

Clinical Manifestations. MPS VII (Sly's disease) has a well-recognized neonatal presentation with nonimmune hydrops fetalis, hepatosplenomegaly, ascites, pitting edema, hernias, skeletal abnormalities (dysostosis multiplex), and corneal clouding. In the most severely affected patients, MPS I (Hurler's syndrome) can present in the neonatal period with an umbilical or inguinal hernia or an excess of mongolian spots. Hearing loss is common. Clinical evidence of heart disease is present in most patients with MPS.

Diagnosis. MPS VII is diagnosed by evaluating the activity of beta-glucuronidase in white blood cells. Urine glycosaminoglycans can also be quantitated.

Management. Management is primarily supportive care and treatment of complications. Range-of-motion exercises are important to preserve joint function and prevent joint stiffness. Recurrent pneumonia is a frequent complication of MPS VII. Development of hydrocephalus often necessitates the insertion of a ventriculoperitoneal shunt. An ophthalmologic examination should be performed to evaluate for corneal clouding and the development of glaucoma.

Glycogen Storage Disease Type II (Pompe's Disease)

Pathophysiology. Glycogen storage disease type II (GSD-II), also called acid maltase deficiency or Pompe's disease, is an inherited disorder of glycogen metabolism resulting from defects in activity of the lysosomal hydrolase acid alpha-glucosidase in all tissues of the body. This enzyme is required for the degradation of a portion of the body's glycogen. Without it, excessive glycogen accumulates within the lysosomes, eventually causing cellular injury, and enlarging and hindering the function of the entire organ, such as the heart. Energy production is not affected, and hypoglycemia does not occur. Pompe's disease has a worldwide incidence of about 1 in 40,000 births (Chien et al., 2009).

Clinical Manifestations. Prominent findings in infants are cardiomyopathy, progressive cardiomegaly, and left ventricular thickening that eventually leads to outflow tract obstruction. Characteristic findings on ECG are large QRS complexes coupled with abnormally short PR interval. The QRS complex is the combination of the Q wave, R wave, and S wave and represents ventricular depolarization. The PR interval is the interval between the beginning of the P wave and the beginning of the QRS complex of an electrocardiogram that represents the time between the beginning of the contraction of the atria and the beginning of the contraction of the ventricles. Other manifestations are hepatomegaly, striking hypotonia, macroglossia, feeding difficulties, and respiratory distress complicated by pulmonary infection.

Diagnosis. Definitive diagnosis requires the measurement of acid alpha-glucosidase activity in cultured skin fibroblasts or white blood cells. Serum creatinine kinase (CK) is elevated (up to 10 times normal). Hepatic enzymes may also be elevated. Newborn screening for Pompe's disease is under study with the hope that presymptomatic diagnosis would permit earlier therapeutic intervention (before extensive muscle damage), leading to better outcomes (Chien et al., 2009).

Management. Until recently, no effective treatment was available for Pompe's disease, and these infants usually succumbed to cardiopulmonary failure. A recombinant version of human alpha-glucosidase, a glycoprotein enzyme needed for breakdown of glycogen in cell lysosomes, has now been developed for treatment of Pompe's disease.

DISORDERS OF CHOLESTEROL SYNTHESIS

Smith–Lemli–Opitz Syndrome

Smith–Lemli–Opitz (SLO) syndrome is a multiple congenital anomalies/mental retardation syndrome caused by an inherited defect in cholesterol biosynthesis. SLO syndrome has an estimated incidence of 1 in 10,000 to 60,000 births (Haas, Herman, & Hoffmann, 2017).

Pathophysiology. The underlying biochemical defect in SLO syndrome is a lack of the microsomal enzyme 3 beta-hydroxysterol-delta 7 reductase (DHCR7), the final enzyme in the sterol biosynthetic pathway that converts 7-dehydrocholesterol (7DHC) to cholesterol. In the absence of DHCR7, the precursor 7DHC accumulates to potentially toxic levels, and insufficient cholesterol is produced. Because cholesterol is required for the development of cell membranes and myelin, and the production of steroid hormones and bile acids, a severe deficiency of cholesterol during morphogenesis is believed to contribute to the abnormalities associated with SLO syndrome. SLO syndrome is different from other disorders of intermediary metabolism, from which the fetus is protected until after birth. Without endogenous cholesterol, the growing embryo depends on maternal cholesterol, which may not be transported across the placenta in sufficient amounts. Thus, the fetus with SLO syndrome suffers systemic and cerebral malformations in proportion to the severity of the deficiency of cholesterol biosynthesis (Quélin et al., 2012).

Clinical Manifestations. Common findings at birth are intrauterine growth restriction, microcephaly, and hypotonia. Facial dysmorphism may feature epicanthic folds, ptosis, anteverted nares, broad nasal tip, micrognathia, and low-set ears. Associated anomalies include syndactyly of the second and third toes (>98%), postaxial polydactyly, small abnormally positioned thumbs, Hirschsprung's disease, and cataracts, and in males, hypospadias, cryptorchidism, and a hypoplastic scrotum. Common clinical manifestations in the newborn include severe hypotonia, feeding difficulties with poor suck and vomiting, and excessive sleepiness with poor responsiveness (Haas et al., 2017). A severe, lethal form of SLO syndrome presents with microcephaly, lethal cardiac and brain anomalies, and ambiguous genitalia (Quélin et al., 2012). These infants expire during the first week of life from multisystem organ failure.

Diagnosis. SLO syndrome is often recognized by its distinctive clinical features. Confirmation is made by finding elevated blood levels of its direct precursor, 7DHC. Plasma cholesterol may be normal or low. Some fetuses with SLO syndrome are identified by anomalies detected prior to birth by ultrasonography, and confirmation can be made by amniotic fluid or chorionic villus sample analysis.

Management. Immediate management is directed toward raising body cholesterol and removing toxic precursors. Providing exogenous cholesterol not only restores low cholesterol levels, but also suppresses the infant's endogenous cholesterol synthesis, decreasing the production of 7DHC (Haas et al., 2017).

DISORDERS OF METAL METABOLISM

Errors of metal metabolism are genetic biochemical disorders in the way that metals are processed by the body: their synthesis, transport, absorption, storage, or utilization.

Molybdenum Cofactor Deficiency

Pathophysiology. The molybdenum cofactor is an essential component of a large family of enzymes involved in important transformations in carbon, nitrogen, and sulfur metabolism. Molybdenum cofactor deficiency is an autosomal recessive, fatal neurologic disorder, characterized by the combined deficiency of sulfite oxidase, xanthine dehydrogenase, and aldehyde oxidase.

Clinical Manifestations. Affected neonates are usually born after an uneventful pregnancy and normal delivery. Soon after birth, feeding difficulties and neurologic symptoms develop. The neurologic picture includes intractable tonic-clonic seizures, axial hypotonia, and peripheral hypertonicity (Koeller & Kaler, 2017). Typical facial features include puffy cheeks, a long philtrum, and a small nose. The neuropathologic findings are consistent with a toxic insult to the brain that causes severe neuronal loss, demyelination of white matter, reactive astrogliosis, and spongiosis. Ectopia lentis (displacement of the lens) may be noted on ophthalmologic examination.

Diagnosis. Molybdenum cofactor deficiency can be difficult to diagnose because there are no clues on routine laboratory studies. A positive sulfite dipstick of fresh urine is suggestive of the disorder; however, a negative test does not rule it out. Urinary S-sulfocysteine, thiosulfate, urothion, xanthine, and hypoxanthine levels aid in the diagnosis of molybdenum cofactor deficiency (Koeller & Kaler, 2017). Plasma uric acid is typically low.

Management. Substitution therapy with purified cyclic pyranopterin monophosphate (cPMP) has been described in the successful treatment of a 6-day-old infant with molybdenum cofactor deficiency (Veldman et al., 2010). No other therapy is currently available for molybdenum cofactor deficiency. One measure that has proved helpful is to limit the intake of sulfur-containing amino acids (cysteine and methionine). Seizures are often difficult to control.

SUMMARY

The number of known inherited disorders of metabolism has risen steadily in recent years and is likely to continue to do so. Although not all will manifest in the neonatal period, many disorders with neonatal onset are rapidly lethal if not recognized and treated without delay. Expanded newborn screening programs have saved many lives through presymptomatic diagnosis, but these programs currently screen for only a fraction of the hundreds of possible metabolic disorders. Neonatal health professionals must be vigilant and consider the diagnosis of an inborn EM in a neonate presenting with clinical manifestations resembling sepsis, or in an infant becoming ill after one or more days of normal health,

particularly when the laboratory data do not fit the clinical picture. Although many neonatal metabolic disorders are not yet amenable to therapy, an exact diagnosis is important for genetic counseling and prenatal diagnostic procedures that the family may desire for future pregnancies.

CASE STUDY

■ **Identification of the Problem.** A newborn infant, just over 48 hours of age, was rooming with his mother, who noted him to be jaundiced and unusually sleepy. His mother could not awaken him to breastfeed and she notified the nurse, who took him to the nursery to check his bilirubin level. His total serum bilirubin was 10.4. However, the infant made no response to having his heel lanced for the blood draw, and the nurse was unable to awaken him to feed. She placed a call to the infant's pediatrician, and a CBC with differential and a blood culture were ordered. The infant was then transferred to the NICU for further evaluation. An intravenous drip of D10W at 100 mL/kg/day was begun, and ampicillin and gentamicin were given. However, the CBC, differential, and C-reactive protein (CRP) were all within normal limits, and subsequently, the blood culture was negative as well.

■ **Assessment: History and Physical Examination.** The infant, a boy, was born by cesarean section to a 33-year-old G3, P2 group B streptococcus (GBS)–negative, insulin-dependent gestational diabetic mother, in satisfactory glucose control during the last trimester of pregnancy. Family history was significant for a maternal brother who died on the third day of life from unknown causes. Siblings of this infant were two healthy girls. This infant's Apgar scores were 8 and 9. Birth weight was 3,790 g. The infant's blood sugar levels on day 1 were all within normal limits; he appeared healthy and roomed in with his mother, breastfeeding on demand with occasional formula supplementation. He was voiding and stooling normally.

On examination, his color was pale pink with mild jaundice on room air. Respirations were regular and rapid, but there were no retractions, grunting, or flaring. His axillary temperature was 97°F, heart rate 122, respiratory rate 80, blood pressure 60/36 (mean 44). Glucose screen (point of care) was 52. An arterial blood gas was obtained, and the results were pH 7.32, Po_2 71, Pco_2 30, base deficit −2. Capillary refill was 2 to 3 seconds, pulses were equal, and there was no murmur. His abdomen was rounded with mild hepatomegaly. He did not react to stimulation of any type and could not be aroused. His overall tone was decreased, he did not suck, and no Moro reflex was noted. Within 24 hours, he began having seizures requiring treatment with phenobarbital. Severe apnea and respiratory failure led to intubation and mechanical ventilation.

■ **Differential Diagnosis.** The chief differential diagnosis for a full-term infant becoming ill at about 48 hours of age is neonatal sepsis, although this mother was GBS negative and the infant's laboratory data did not support this diagnosis. His serum bilirubin was not high enough to explain his somnolence and lethargy as stemming from bilirubin encephalopathy. Transient tachypnea of the newborn was unlikely, because he did not appear to be in any significant respiratory distress other than his rapid respiratory rate, and the clinical picture was more consistent with a neurologic insult. The history did not suggest an etiology for neonatal encephalopathy. The next most likely diagnostic possibilities would be inborn errors of intermediary metabolism that present with an "intoxication" syndrome and without hypoglycemia, following a symptom-free interval: organic acid disorders, amino acid disorders, and UCDs.

■ **Diagnostic Tests.** To start differentiating between the most likely categories of metabolic disorders, a blood ammonia level is needed. Depending on this result, other important diagnostic tests might include electrolytes, BUN, creatinine, quantitative plasma, and urine amino acids, urine organic acids, and urine orotic acid.

■ **Working Diagnosis.** The infant's blood ammonia level was 1,901 µmol/L. This suggests a working diagnosis of a urea cycle defect. Additional testing revealed the following:

Plasma amino acids: Glutamine 1,632 µmol/L (reference range 376–709 µmol/L)

Citrulline trace (reference range 10–45 µmol/L)

Urine orotic acid: 852 mmol/mol creatinine (reference range 0.12–3.07 mmol/mol creatinine)

Following the algorithm for neonatal hyperammonemia (see Figure 9.2), these findings point to a working diagnosis of OTC deficiency. In support of this diagnosis, the infant's symptoms began after 24 hours of age, and he had no significant acidosis.

■ **Development of Management Plan.** The most urgent priority was reduction of the baby's toxic blood ammonia level. In addition, all protein intake had to be stopped temporarily until the blood ammonia level was normalized; so, the baby was made NPO and no amino acids were added to the intravenous solution. Protein would be reintroduced within 48 hours in small yet sufficient amounts to prevent catabolism. While preparations were being made for hemodialysis, an umbilical venous catheter was inserted for administration of "scavenger drugs," or agents that supply alternatives to urea for elimination of waste nitrogen.

■ **Implementation and Evaluation of Effectiveness.** A loading dose of sodium phenylacetate plus sodium benzoate 2.5 mL/kg was given via central catheter over 90 minutes (Ammonul, Ucyclyd Pharma, Scottsdale, AZ). In addition, a dose of arginine HCl 10% (2.0 mL/kg) was administered. Hemodialysis was initiated, and after about 36 hours, the infant's ammonia level was successfully reduced to less than 70 µmol/L. He showed rapid improvement in neurologic status and was extubated. Amino acids were reintroduced to the intravenous solution after another 24 hours, and feedings were restarted shortly thereafter with citrulline supplementation. Following discharge, he was maintained on this regimen, plus pharmacologic diversion therapy, and he had two metabolic crises requiring hospitalization before receiving a liver transplant. An MRI of his brain at 1 year of age revealed that the neurologic prognosis remains guarded. The family also underwent genetic counseling regarding recurrence risks and prenatal genetic diagnosis for future pregnancies.

EVIDENCE-BASED PRACTICE BOX

Hyperammonemia (plasma ammonium level >150 μmol/L or >260 mcg/dL) is a metabolic disturbance that is a characteristic feature of many different EMs, including disorders of organic acids, fatty acid oxidation, and the urea cycle. Ammonia, a product of protein metabolism, is a neurotoxin that can accumulate in the brain along with glutamine, resulting in osmotic swelling, brain edema, and permanent brain damage.

Many areas of the developing brain are vulnerable to the effects of excess ammonia, and the neurologic sequelae are correlated with the duration and magnitude of hyperammonemia (Braissant, 2010). Therefore, the prevention or reversal of hyperammonemic coma is of prime concern in a suspected metabolic disorder. The initial management of ammonia encephalopathy must often proceed in the absence of a definitive diagnosis (Westrope, Morris, Burford, & Morrison, 2010). The kidneys clear ammonia poorly, so removal of ammonia from the body must be expedited by another method. Two means of accomplishing this are diversion therapy using ammonia-scavenging drugs, and physical removal of ammonia from the circulation with dialysis or hemofiltration.

Although the efficacy of dialysis or hemofiltration in the clearance of serum ammonia has been established, the optimal treatment modality has not. Few published studies have shown associations between specific dialysis modalities and survival rates. Owing to the rarity of the EMs, randomized controlled trials to compare these therapies do not exist. The evidence is largely retrospective and observational, from single case reports and case series.

Expert consensus suggests that first-line treatment of hyperammonemia should involve stopping protein intake, suppressing protein catabolism, and administering agents that combine with ammonia to form compounds with high renal clearance. Many case reports describe successful medical treatment of newborns with various EMs using N-carbamylglutamate (Filippi et al., 2010; Gessler, Buchal, Schwenk, & Wermuth, 2010; Kasapkara et al., 2011), sodium benzoate, and sodium phenylbutyrate. When plasma ammonia levels decline within 4 hours of treatment, the need for dialysis may be averted (Picca et al., 2001). During this 4-hour window, however, preparations should be underway to institute a more aggressive route of ammonia clearance in neonates who do not respond to medical treatment (Picca, Bartuli, & Dionisi-Vici, 2008).

If detoxification with ammonia-scavenging drugs fails to reduce the plasma ammonia level within a few hours, another method of clearance must be initiated without delay. Options include hemodialysis, continuous venovenous hemofiltration (CVVHF), continuous venovenous hemodialysis (CVVHD), and peritoneal dialysis. Methods that provide continuous renal replacement (hemodialysis or hemofiltration) are preferred over peritoneal dialysis, although evidence is scant. Picca et al. (2001) reported their experience using three different extracorporeal methods of clearing ammonia (continuous arteriovenous hemodialysis, CVVHD, and hemodialysis). They found that CVVHD was the most effective method to promptly lower ammonia levels. However, they also found that the most relevant indicator of prognosis was not how quickly the plasma ammonia level was reduced, but the duration of hyperammonemic coma before the initiation of dialysis (Picca et al., 2001). In particular, coma duration longer than 30 hours before dialysis initiation negatively affects the outcome (Picca et al., 2001). Therefore, they recommend that infants with rising ammonia levels should be transferred without delay to a facility capable of providing extracorporeal dialysis if medical therapy fails.

In a 10-year experience with CVVHF to treat hyperammonemia, Westrope et al. (2010) found this method to be safe, effective, and efficient in lowering plasma ammonia levels. However, neither the pretreatment ammonia level nor the speed of ammonia removal was associated with outcome (Westrope et al., 2010). This study suggests that the pretreatment status of the neonate may be the main determinant of outcome, reinforcing the need to initiate medical treatment and to proceed with continuous renal replacement therapy without delay.

In another series of 21 children (15 neonates), investigators retrospectively analyzed outcomes for patients receiving CVVHD or peritoneal dialysis (Arbeiter et al., 2010). A 50% reduction in serum ammonia levels was achieved significantly faster with CVVHD than with peritoneal dialysis. In neonatal patients, survival and survival without mental retardation were both better following CVVHD, although the sample sizes were small and the duration of pretreatment encephalopathy was not known. Of interest, these investigators documented the best outcomes in patients with neonatal-onset citrullinemia.

Although it would be desirable to have randomized, controlled trial evidence of the superiority of one method of treating hyperammonemia over another, the trend toward presymptomatic detection of metabolic disorders could, in the future, lead to preventive treatments that will obviate the need for such aggressive approaches to hyperammonemia. In the meantime, clinicians should continue to collect data on the few patients encountered with these disorders to inform best practice and improve outcomes.

References

Arbeiter, A. K., Dranz, B., Wingen, A. M., Bonzel, K. E., Dohna-Schwake, C., Hanssle, L., . . . Büscher, R. (2010). Continuous venovenous haemodialysis (CVVHD) and continuous peritoneal dialysis (CPD) in the acute management of 21 children with inborn errors of metabolism. *Nephrology Dialysis and Transplantation*, *25*, 1257–1265. doi:10.1093/ndt/gfp595

Braissant, O. (2010). Current concepts in the pathogenesis of urea cycle disorders. *Molecular Genetics and Metabolism, 100*, S3–S12. doi:10.1016/j.ymgme.2010.02.010

Filippi, L., Gozini, E., Fiorini, P., Malvagia, S., la Marca, G., & Donati, M. A. (2010). N-carbamylglutamate in emergency management of hyperammonemia in neonatal acute onset propionic and methylmalonic aciduria. *Neonatology, 97*, 286–290. doi:10.1159/000255168

Gessler, P., Buchal, P., Schwenk, H. U., & Wermuth, B. (2010). Favourable long-term outcome after immediate treatment of neonatal hyperammonemia due to N-acetyl glutamate synthase deficiency. *European Journal of Pediatrics, 169*, 197–199. doi:10.1007/s00431-009-1006-0

(*continued*)

EVIDENCE-BASED PRACTICE BOX (*continued*)

Kasapkara, C. S., Ezgu, F. S., Okur, I., Tumer, L., Biberoglu, G., & Hasanoglu, A. (2011). N-carbamylglutamate treatment for acute neonatal hyperammonemia in isovaleric acidemia. *European Journal of Pediatrics, 270*, 799–801. doi:10.1007/s00431-010-1362-9

Picca, S., Bartuli, A., & Dionisi-Vici, C. (2008). Medical management and dialysis therapy for the infant with an inborn error of metabolism. *Seminars in Nephrology, 28*, 477–480. doi:10.1016/j.semnephrol.2008.05.007

Picca, S., Dionisi-Vici, C., Abeni, D., Pastore, A., Rizzo, C., Orzalesi, M., . . . Bartuli, A. (2001). Extracorporeal dialysis in neonatal hyperammonemia: Modalities and prognostic indicators. *Pediatric Nephrology, 16*, 862–867. doi:10.1007/s004670100702

Westrope, C., Morris, K., Burford, D., & Morrison, G. (2010). Continuous hemofiltration in the control of neonatal hyperammonemia: A 10-year experience. *Pediatric Nephrology, 25*, 1725–1730. doi:10.1007/s00467-010-1549-3

PARENT VOICES

Jimena Guild

The simple act of feeding my child seems ordinary to most parents, but for us whose child suffered from feeding issues, it was huge. My son Kai was born premature at 28 weeks and developed acute oral aversion among other issues during his 4-month stay in the NICU. To ensure he received the necessary nutrition, my son was fed through a tube that from his nose fed right into his stomach called a nasal gastric (NG) tube. In the NICU, he fought the bottle so much I was not even going to try him on the breast. He continued to struggle with drinking from a bottle for the first 6 months of his life. He was labeled "failure to thrive" and needed assistance from nursing services and an O.T. who would come to help him develop the skills he needed to eat orally. Kai was tube-fed for the first 2 years of his life. Most parents whose children have feeding tubes do not know for how long their child will need the tube. We were lucky that he only had it for 2 years; he will never remember the awful nights we would struggle to get the tube put back in when he would pull it out; the screams, the cries, from both of us were not something I wish on any parent; having to hold him down while my husband fished the tube down into his stomach, sometimes having to redo it multiple times if it went down the wrong tube (into his lungs) or came out of his mouth as he coughed. Those are days I will never forget, but it's also important to know that feeding tubes offer hope. Sure, it's an alternative way of eating by mouth, but it is one that gives children—and all people—with no other alternative, a way to thrive. Nowadays, Kai is a healthy little 7-year-old boy who, you wouldn't believe, has an insatiable hunger; he is the most nonpicky child you will meet and is willing to try anything and everything once.

ONLINE RESOURCES

National Center for Advancing Translational Sciences-Office of Rare Diseases Research. Retrieved from https://ncats.nih.gov/about/center/org/ordr

National Newborn Screening and Global Resource Center. Retrieved from https://genes-r-us.uthscsa.edu/

Orphanet. Retrieved from http://www.orpha.net/consor/cgi-bin/index.php

REFERENCES

Ah Mew, N., Kimpson, K. L., Gropman, A. L., Lanpher, B. C., Chapman, K. A., & Summar, M. L. (2017). In M. P. Adam, H. H. Ardinger, R. A. Pagon, & S. E. Wallace (Eds.). GeneReviews® [Internet]. Seattle: University of Washington, Seattle. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK1217

Berry, G. T. (2012). Galactosemia: When is it a newborn screening emergency? *Molecular Genetics and Metabolism, 106*(1), 7–11. doi:10.1016/j.ymgme.2012.03.007

Ah Mew, N., McCarter, R., Daikhin, Y., Nissim, I., Yudkoff, M., & Tuchman, M. (2010). N-carbamylglutamate augments ureagenesis and reduces ammonia and glutamine in propionic acidemia. *Pediatrics, 126*, e208–e214. doi:10.1542/peds.2010-0008

Arnold, C. L., Davis, T. C., Frempong, J. O., Humiston, S. G., Bocchini, A., Kennen, E. M., & Lloyd-Puryear, M. (2006). Assessment of newborn screening parent education materials. *Pediatrics, 117*(Suppl. 3), S320–S325. doi:10.1542/peds.2005-2633L

Braissant, O. (2010). Current concepts in the pathogenesis of urea cycle disorders. *Molecular Genetics and Metabolism, 100*(Suppl.), S3–S12. doi:10.1016/j.ymgme.2010.02.010

Brown, G. (2012). Pyruvate dehydrogenase deficiency and the brain. *Developmental Medicine and Child Neurology, 54*, 395–396. doi:10.1111/j.1469-8749.2012.04266.x

Burton, B. K. (2000). Urea cycle disorders. *Clinics in Liver Disease, 4*, 815–830. doi:10.1016/S1089-3261(05)70143-4

Cederbaum, S. (2018). Introduction to metabolic and biochemical genetic disease. In C. A. Gleason & S. E. Juul (Eds.), *Avery's diseases of the newborn* (10th ed., pp. 224–229). Philadelphia, PA: Elsevier.

Campeau, P. M., Pivalizza, P. J., Miller, G., McBride, K., Karpen, S., Goss, J., & Lee, B. H. (2010). Early orthotopic liver transplantation in urea cycle

defects: Follow up of a developmental outcome study. *Molecular Genetics and Metabolism, 100*(Suppl.), S85–S87. doi:10.1016/j.ymgme.2010.02.012

Chapman, K. A., Gropman, A., MacLeod, E., Stagni, K., Summar, M. L., Ueda, K., . . . Chakrapani, A. (2012). Acute management of propionic acidemia. *Molecular Genetics and Metabolism, 105*, 16–25. doi:10.1016/j.ymgme.2011.09.026

Chien, Y. H., Lee, N. C., Thurberg, B. L., Chiang, S. C., Zhang, X. K., Keutzer, J., ... Hwu, W. L. (2009). Pompe disease in infants: Improving the prognosis by newborn screening and early treatment. *Pediatrics, 124*, e1116–e1125. doi:10.1542/peds.2008-3667

Cleary, M. A. (2010). Phenylketonuria. *Paediatrics and Child Health, 21*(2), 61–64. doi:10.1016/j.paed.2010.08.015

Daniotti, M., la Marca, G., Fiorini, P., & Filippi, L. (2011). New developments in the treatment of hyperammonemia: Emerging use of carglumic acid. *International Journal of Genetics in Medicine, 4*, 21–28. doi:10.2147/IJGM.S10490

Davis, T. C., Humiston, S. G., Arnold, C. L., Bocchini, J. A., Bass, P. F. III, Kennen, E. M., . . . Lloyd-Puryear, M. (2006). Recommendations for effective newborn screening communication: Results of focus groups with parents, providers, and experts. *Pediatrics, 117*(Suppl. 3), S326–S340. doi:10.1542/peds.2005-2633M

Davison, J. E., Davies, N. P., Wilson, M., Sun, Y., Chakrapani, A., McKiernan, P. J., . . . Peet, A. C. (2011). MR spectroscopy-based brain metabolite profiling in propionic acidaemia: Metabolic changes in the basal ganglia during acute decompensation and effect of liver transplantation. *Orphanet Journal of Rare Diseases, 6*, 19. doi:10.1186/1750-1172-6-19

Ensenauer, R., Fingerhut, R., Maier, E. M., Polanetz, R., Olgemöller, B., Röschinger, W., & Muntau, A. C. (2011). Newborn screening for isovaleric acidemia using tandem mass spectrometry: Data from 1.6 million newborns. *Clinical Chemistry, 57*, 623–626. doi:10.1373/clinchem.2010.151134

Filippi, L., Gozzini, E., Fiorini, P., Malvagia, S., la Marca, G., & Donati, M. A. (2010). Carbamylglutamate in emergency management of hyperammonemia in neonatal acute onset propionic and methylmalonic aciduria. *Neonatology, 97*, 286–290. doi:10.1159/000255168

Gibson, K. M., Van Hove, J. L. K., Willemsen, M. A. A. P., & Hoffmann, G. F. (2017). Neurotransmitter disorders. In K. Sarafoglou, G. F. Hoffman, & K. S. Roth (Eds.), *Pediatric endocrinology and inborn errors of metabolism* (2nd ed., pp. 1057–1094). New York, NY: McGraw Hill.

Grünert, S., Wendel, U., Lindner, M., Leichsenring, M., Schwab, K. O., Vockley, J., . . . Ensenauer, R. (2012). Clinical and neurocognitive outcome in symptomatic isovaleric acidemia. *Orphanet Journal of Rare Diseases, 7*, 9. doi:10.1186/1750-1172-7-9

Haas, D., Herman, G. E., & Hoffmann, G. F. (2017). Defects of cholesterol biosynthesis. In K. Sarafoglou, G. F. Hoffmann, & K. S. Roth (Eds.), *Pediatric endocrinology and inborn errors of metabolism* (2nd ed., pp. 413–426). New York, NY: McGraw-Hill.

Hendriksz, C. J., & Gissen, P. (2010). Glycogen storage disease. *Paediatrics and Child Health, 12*, 2. doi:10.1016/j.paed.2010.09.013

Hertzberg, V. S., Hinton, C. F., Therrell, B. L., & Shapira, S. K. (2011). Birth prevalence rates of newborn screening disorders in relation to screening practices in the United States. *Journal of Pediatrics, 159*, 555–560. doi:10.1016/j.jpeds.2011.04.011

Hoffmann, G. F., Burlina, A., & Barshop, B. A. (2017). Organic acidurias. In K. Sarafoglou, G. F. Hoffmann, & K. S. Roth (Eds.), *Pediatric endocrinology and inborn errors of metabolism* (2nd ed., pp. 209–250). New York, NY: McGraw-Hill.

Jameson, E., & Walter, J. H. (2010). Medium-chain acyl-CoA dehydrogenase deficiency–A review. *Paediatrics and Child Health, 21*(2), 90–93. doi:10.1016/j.paed.2010.09.010

Johnson, J. A., Le, K. L., & Palacios, E. (2009). Propionic acidemia: Case report and review of neurologic sequelae. *Pediatric Neurology, 40*, 317–320. doi:10.1016/j.pediatrneurol.2008.10.021

Kasapkara, C. S., Ezgu, F. S., Okur, I., Tumer, L., Biberoglu, G., & Hasanoglu, A. (2011). *N*-carbamylglutamate treatment for acute neonatal hyperammonemia in isovaleric acidemia. *European Journal of Pediatrics, 170*, 799–801. doi:10.1007/s00431-010-1362-9

Kilicarslan, R., Alkan, A., Demirkol, D., Toprak, H., & Sharifov, R. (2012, April 3). Maple syrup urine disease: Diffusion-weighted MRI findings during acute metabolic encephalopathic crisis. *Japanese Journal of Radiology, 30*(6), 522–525. doi:10.1007/s11604-012-0079-2

Koeller, D. M., & Kaler, S. G. (2017). Disorders of mineral metabolism (iron, copper, zinc, and molybdenum). In K. Sarafoglou, G. F. Hoffmann, & K. S. Roth (Eds.), *Pediatric endocrinology and inborn errors of metabolism* (2nd ed., pp. 875–894). New York, NY: McGraw-Hill.

Kumar, V., Abbas, A. K., Fausto, N., & Aster, J. (Eds.). (2009). *Robbins and Cotran: Pathologic basis of disease* (8th ed.). Philadelphia, PA: Elsevier.

Leonard, J. V., & Morris, A. A. M. (2006). Diagnosis and early management of inborn errors of metabolism presenting around the time of birth. *Acta Paediatrica, 95*, 6–14. doi:10.1080/08035250500349413

Leonard, J. V., & Morris, A. A. M. (2010). The investigation and initial management of children with suspected metabolic disease. *Paediatrics and Child Health, 21*, 51–55. doi:10.1016/j.paed.2010.08.014

Marin-Valencia, I., Roe, C. R., & Pascual, J. M. (2010). Pyruvate carboxylase deficiency: Mechanisms, mimics, and anaplerosis. *Molecular Genetics and Metabolism, 101*, 9–17. doi:10.1016/j.ymgme.2010.05.004

McGuire, P. J. (2017). Metabolism Infection Immunity (MINI) Study. *National Human Genome Research Institute*. Retrieved from https://www.genome.gov/27551371/the-nih-mini-study-metabolism-infection-and-immunity-in-inborn-errors-of-metabolism

Merritt, J. L., & Gallagher, R. C. (2018). Inborn errors of carbohydrate, ammonia, amino acid, and organic acid metabolism. In S. C. A. Gleason & S. E. Juul (Eds.), *Avery's diseases of the newborn* (10th ed., pp. 230–252). Philadelphia, PA: Elsevier. Retrieved from https://www.semanticscholar.org/paper/Inborn-Errors-of-Carbohydrate%2C-Ammonia%2C-Amino-Acid%2C-Merritt-Gallagher/2b5730e59d7cbf7a1e5bdac6b1c08328c54a8082

Morris, A. M. M., & Chakrapani, A. (2017). Tyrosinemia and other disorders of tyrosine degradation. In K. Sarafoglou, G. F. Hoffman, & K. S. Roth (Eds.), *Pediatric endocrinology and inborn errors of metabolism* (2nd ed., pp. 267–276). New York, NY: McGraw-Hill.

Mussa, A., Porta, F., Hoffmann, G. F., & Sarafoglou, K. (2017). Emergency assessment and management of suspected inborn errors of metabolism and endocrine disorders. In K. Sarafoglou, G. F. Hoffmann, & K. S. Roth (Eds.), *Pediatric endocrinology and inborn errors of metabolism* (2nd ed., pp. 25–42). New York, NY: McGraw-Hill.

Patel, K. P., O'Brien, T. W., Subramony, S. H., Shuster, J., & Stacpoole, P. W. (2012). The spectrum of pyruvate dehydrogenase complex deficiency: Clinical, biochemical and genetic features in 371 patients. *Molecular Genetics and Metabolism, 105*, 34–43. doi:10.1016/j.ymgme.2011.09.032

Puffenberger, E. G. (2003). Genetic heritage of the old order Mennonites of southeastern Pennsylvania. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics, 121C*, 18–31. doi:10.1002/ajmg.c.20003

Quélin, C., Loget, P., Verloes, A., Bazin, A., Bessières, B., Laquerrière, A., . . . Gonzales, M. (2012). Phenotypic spectrum of fetal Smith-Lemli-Opitz syndrome. *European Journal of Medical Genetics, 55*, 81–90. doi:10.1016/j.ejmg.2011.12.002

Rector, R. S., & Ibdah, J. A. (2010). Fatty acid oxidation disorders: Maternal health and neonatal outcomes. *Seminars in Fetal and Neonatal Medicine, 15*, 122–128. doi:10.1016/j.siny.2009.10.006

Rice, G. M., & Steiner, R. D. (2016). Inborn errors of metabolism (metabolic disorders). *Pediatrics in Review, 37*(1), 3–17. doi:10.1542/pir.2014-0122

Romano, S., Valayannopoulos, V., Touati, G., Jais, J. P., Rabier, D., de Keyzer, Y., . . . de Lonlay, P. (2010). Cardiomyopathies in propionic aciduria are reversible after liver transplantation. *Journal of Pediatrics, 156*, 128–134. doi:10.1016/j.jpeds.2009.07.002

Scott, C., & Olpin, S. (2010). Peroxisomal disorders. *Paediatrics and Child Health, 21*, 71–75. doi:10.1016/j.paed.2010.08.013

Sharma, R., Sharrard, M. J., Connolly, D. J., & Mordekar, S. R. (2012). Unilateral periventricular leukomalacia in

association with pyruvate dehydrogenase deficiency. *Developmental Medicine and Child Neurology, 54*, 469–471. doi:10.1111/j.1469-8749.2011.04108.x

Shekhawat, P., Bennett, M. J., Sadovsky, Y., Nelson, D. M., Rakheja, D., & Strauss, A. W. (2003). Human placenta metabolizes fatty acids: Implications for fetal acid oxidation disorders and maternal liver diseases. *American Journal of Physiology, Endocrinology & Metabolism, 284*, E1098–E1105. doi:10.1152/ajpendo.00481.2002

Spiekerkoetter, U., Bastin, J., Gillingham, M., Morris, A., Wijburg, F., & Wilcken, B. (2010). Current issues regarding treatment of mitochondrial fatty acid oxidation disorders. *Journal of Inherited Metabolic Disease, 33*, 555–561. doi:10.1007/s10545-010-9188-1

Stockler, S., Moeslinger, D., Herle, M., Wimmer, B., & Ipsiroglu, O. S. (2012). Cultural aspects in the management of inborn errors of metabolism. *Journal of Inherited Metabolic Disease, 35*(6), 1147–1152. doi:10.1007/s10545-012-9455-4

Summar, M. L., Dobbelaere, D., Brusilow, S., & Lee, B. (2008). Diagnosis, symptoms, frequency, and mortality of 260 patients with urea cycle disorders from a 21-year multicentre study of acute hyperammonaemic episodes. *Acta Paediatrica, 97*, 1420–1425. doi:10.1111/j.1651-2227.2008.00952.x

Thomas, J. A., Lam, C., & Berry, G. T. (2018). Lysosomal storage, peroxisomal and glycosylation disorders and Smith-Lemli-Opitz syndrome in the neonate. In C. A. Gleason & S. E. Juul (Eds.), *Avery's diseases of the newborn* (10th ed., pp. 253–272). Philadelphia, PA: Elsevier.

Tuchman, M., Caldovic, L., Daikhin, Y., Horryn, O., Nissim, I, Nissim, I., . . . Yudkoff, M. (2008). *N*-carbamylglutamate markedly enhances ureagenesis in *N*-acetylglutamate deficiency and propionic acidemia as measured by isotopic incorporation and blood biomarkers. *Pediatric Research, 64*, 213–217. doi:10.1203/PDR.0b013e318179454b

U.S. Department of Health and Human Services. (2018, July). *Recommended uniform screening panel*. Retrieved from http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/recommendedpanel/index.html

Veldman, A., Santamaria-Araujo, J. A., Sollazzo, S., Pitt, J., Gianello, R., Yaplito-Lee, J., . . . Schwarz, G. (2010). Successful treatment of molybdenum cofactor deficiency type A with cPMP. *Pediatrics, 125*, e1249–e1254. doi:10.1542/peds.2009-2192

Vockley, J., Longo, N., Andresen, B. S., & Bennett, M. J. (2017). Mitochondrial fatty acid oxidation disorders. In K. Sarafoglou, G. F. Hoffmann, & K. S. Roth (Eds.), *Pediatric endocrinology and inborn errors of metabolism* (2nd ed., pp. 125–144). New York, NY: McGraw-Hill.

Wilcken, B. (2010). Fatty acid oxidation disorders: Outcome and long-term prognosis. *Journal of Inherited Metabolic Diseases, 33*, 501–506. doi:10.1007/s10545-009-9001-1

Wraith, J. E. (2002). Lysosomal disorders. *Seminars in Neonatology, 7*, 75–83. doi:10.1053/siny.2001.0088

Wraith, J. E. (2010). Lysosomal disorders. *Paediatrics and Child Health, 21*, 76–79. doi:10.1016/j.paed.2010.08.012

Yudkoff, M., Summar, M. L., & Haberle, J. (2017). Urea cycle disorders. In K. Sarafoglou, G. F. Hoffmann, & K. S. Roth (Eds.), *Pediatric endocrinology and inborn errors of metabolism* (2nd ed., pp. 191–208). New York, NY: McGraw-Hill.

CHAPTER 10

Endocrine System

Susan Kau and Stephanie Hoe

INTRODUCTION

Our understanding of endocrine disorders in the neonate advances to the molecular level in parallel with discoveries in genetics and cell biology. Endocrine processes are fundamental to growth and development of the fetus and newborn. Prompt recognition of endocrine disorders in the neonate is the chief prerequisite in our ability to institute life-saving treatment and minimize long-term morbidity. This chapter provides an overview of the clinical endocrine disorders that may be seen in the neonatal period.

THE ENDOCRINE SYSTEM

The word *endocrine*, from the Greek words *endo* (within) and *krinein* (to separate), describes a diverse group of ductless organs that secrete hormones directly into the bloodstream. The classic endocrine glands are the hypothalamus, pineal, pituitary, thyroid, parathyroid, thymus, pancreatic islet cells, adrenals, ovaries, and testes, although the heart, kidneys, and intestines also secrete and regulate hormones. Among the many functions of the endocrine system are coordination and regulation of metabolism and energy, the internal environment, growth and development, and sexual differentiation and reproduction. Maintenance of homeostasis (the metabolic milieu of the body in a steady state) is considered the most important function of the endocrine system (Bethin & Fuqua, 2014).

The endocrine glands synthesize, store, and secrete hormones, the chemical messengers, or signals, of the endocrine system, that are responsible for tight regulation of diverse physiologic functions. Hormones are peptides, amines, or steroids and are further classified as either regulatory or effector hormones (Bethin & Fuqua, 2014). Secreted into the blood or extracellular fluid, hormones exert their actions on specific cells, either locally or in distant tissues called target cells. Target cells respond to hormones that contain receptors for those precise hormones. Hormones must first bind to these receptor sites before exerting physiologic actions. Some hormones, such as insulin, are fully active on release into the circulatory system, whereas others, such as T_4, require activation to produce their biologic effects. Hormones that must be modified to active hormone after synthesis are known as prepro- or prohormones.

Many hormones are insoluble in water and must be bound to carrier proteins to be transported in the circulatory system. These protein-bound hormones exist in rapid equilibrium with minute quantities of hormone that remain in the aqueous plasma. This "free" fraction of the circulating hormone is taken up by the cell and represents the active hormone concentration that provides feedback to regulate synthesis of the new hormone.

Target hormone levels also serve as powerful negative feedback regulators of their own production via suppression of trophic hormones and hypothalamic releasing hormones. As the target hormone level rises, a message is sent to the anterior pituitary to reduce production of the respective trophic hormone, and also to the hypothalamus to slow production of the respective releasing hormone. Endocrine disease has traditionally been classified as hormone excess, hormone deficiency, or altered tissue responses to hormones (e.g., hormone resistance). Clinical endocrine abnormalities can also be driven by deviations in the feedback systems that control hormone levels. An explosion of new data from molecular genetic studies is redefining "endocrine disease" as a broad array of mutations and alterations in expression of thousands of genes that result in either "loss of function" or "gain of function"; in other words, hyposecretory or hypersecretory disorders (Tenore & Driul, 2009).

Development of the fetal endocrine system is more or less independent of maternal endocrine influences (Divall & Merjaneh, 2018). The placenta blocks the entry of most maternal hormones into the fetal circulation, but the minute quantities that do achieve transplacental passage can have profound effects. Some of these prenatal exposures are essential to fetal growth and development; others may contribute to fetal and neonatal endocrine dysfunction.

FETAL ORIGINS OF ADULT DISEASE

The intrauterine endocrine milieu can have powerful effects on growth and development of the fetal endocrine system. When exposed to a variety of different stressors (maternal undernutrition, uteroplacental insufficiency, or psychological stress), the fetus releases glucocorticoids and catecholamines that, during critical periods of development, affect the development of the fetal hypothalamic–pituitary–adrenal (HPA) axis. Chronic stress can also induce intrauterine growth restriction, or the so-called thrifty phenotype, in the fetus, an adaptation to the limited supply of nutrients (Divall & Merjaneh, 2018). The way in which the fetus adapts, a concept known as programming, is believed to permanently alter physiology and metabolism. Permanent alterations in

fetal metabolic programming contribute to endocrine, metabolic, and cardiovascular disease in adult life (Seki, Williams, Vuguin, & Charron, 2012).

NEONATAL ENDOCRINE DISORDERS

Many neonatal endocrine disorders originate in developmental defects of, or injury to, the endocrine glands (Bethin & Fuqua, 2014). Endocrinopathy in the newborn can be caused by a mutation in a single gene or by genomic imprinting, when the expression of the gene depends on which parent passed on that particular gene (Divall & Merjaneh, 2018). In addition to well-described neonatal endocrine disorders such as hypothyroidism and congenital adrenal hyperplasia (CAH), endocrine dysfunction can affect the preterm infant in a variety of ways as a function of maturation. Exposure to various exogenous agents in the environment, known as *endocrine disruptors,* can have deleterious effects on the development of the endocrine system. Numerous chemicals have known estrogenic or antiandrogenic properties and have been shown to disturb sexual differentiation in animals (Divall & Merjaneh, 2018). The extent to which endocrine disruptors are responsible for increases in hypospadias and testicular dysgenesis syndrome in humans that have been reported in some parts of the world is unknown.

PITUITARY GLAND AND HYPOTHALAMUS

The pituitary gland is the master gland; it produces and secretes hormones, and sends signals to the other glands. The pituitary gland has two distinct structures, the anterior and posterior pituitary, with different embryologic origins. The anterior pituitary develops from oral ectoderm, a diverticulum called Rathke's pouch, and its cells differentiate into specific hormone-secreting cells. The posterior pituitary develops from neuroectoderm evaginating ventrally from the developing brain. The two tissues grow together into a single gland but remain functionally separate.

The hypothalamus, located just above the pituitary gland, secretes the releasing and inhibiting hormones that in turn influence the production of anterior pituitary hormones. Hypothalamic hormones are carried to the anterior pituitary via hypothalamic–hypophyseal portal veins where they bind to receptors on the anterior pituitary cells. The anterior pituitary regulates growth, differentiation, and homeostasis and produces growth hormone, prolactin, adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH). Hormones secreted by the posterior pituitary include oxytocin and hypothalamic-produced vasopressin (antidiuretic hormone, ADH). The hypothalamus is the interface between the endocrine and autonomic nervous systems.

ANTERIOR PITUITARY DISORDERS

Congenital Hypopituitarism

Congenital hypopituitarism, although rare in the newborn, has a number of possible etiologies. Some cases of congenital hypopituitarism are attributed to mutations in genes encoding transcription factors involved in pituitary gland development (Alatzoglou & Dattani, 2009). Congenital hypopituitarism can be an isolated defect, or it can be associated with malformations including holoprosencephaly, septo-optic dysplasia, and other midline cerebral anomalies, the same developmental defects of the embryonic brain that lead to hypothalamic dysfunction. Infection and hypovolemic shock stemming from birth-related complications such as placenta previa and abruptio placentae are additional etiologies.

Pathophysiology. Complete absence of the pituitary gland (pituitary agenesis) and other pituitary lesions can produce deficiencies of one or all pituitary hormones. Panhypopituitarism is a deficiency of all pituitary hormones. In the newborn, the foremost effect of congenital hypopituitarism is hypoglycemia. Owing to the absence of growth hormone, and possibly cortisol as well, insulin is unopposed, placing the neonate at risk for hypoglycemia. Deficiency of growth hormone, and often gonadotropin, combine to stunt penile growth in utero; this is usually referred to as *hypogonadotropic hypogonadism*. Although fetal pituitary growth hormone is not the primary stimulus for fetal growth, growth hormone does make an important contribution to birth size.

Clinical Manifestations. Neonates with congenital hypopituitarism can initially be asymptomatic, with evidence of pituitary hormone deficiencies developing over time (Alatzoglou & Dattani, 2009). Neonates with hypopituitary syndromes can present with midline craniofacial defects such as cleft lip, cleft palate, or bifid uvula. Males may have a micropenis, defined as a normally formed and proportioned penis with a stretched penile length more than two standard deviations below the mean for age. Average penile length for preterm infants 30 weeks of age or older is 2.5 + 0.4 cm and for term infants 3.5 + 0.4 cm. For preterm infants 24 to 26 weeks gestation, the following formula can be used: penile length in centimeters = 2.27 + 0.16 × (gestational age in weeks) (Tuladhar, Davis, Batch, & Doyle, 1998). Hypoglycemia can be mild or severe and persistent. Later in the neonatal period, infants may present with prolonged jaundice and direct hyperbilirubinemia, or evidence of other endocrinopathy, such as diabetes insipidus (DI; high urine output, dehydration, hypernatremia).

Diagnosis. A pediatric endocrinologist usually coordinates the diagnostic testing and interpretation for these infants. The aim of laboratory testing is to determine which hormone deficiencies are present. Measurement of growth hormone, thyroid hormone, and cortisol is essential. MRI of the brain is used to define the anatomy and look for a structural cause of hypopituitarism. For infants with suspected septo-optic dysplasia, an ophthalmologic examination is indicated.

Management. The immediate goals of management are to stabilize the neonate's blood sugar and ensure that the neonate is not at risk for life-threatening cortisol insufficiency. Hypoglycemia might not resolve without growth hormone replacement. Further treatment is geared toward correcting specific hormonal deficiencies. The infant will require follow-up management by the pediatric endocrinologist throughout hospitalization and after discharge.

POSTERIOR PITUITARY DISORDERS

Diabetes Insipidus

DI is a deficiency of ADH (vasopressin). In neonates, central or neurogenic DI can be associated with congenital midline anatomic defects (septo-optic dysplasia, holoprosencephaly), central nervous system (CNS) injury such as intracranial hemorrhage or hypoxia, neoplasms, or it can be idiopathic. As many as 90% of neonates with inherited nephrogenic DI are boys with an X-linked form caused by mutations in the *arginine vasopressin receptor 2* (*AVP2R*) gene, a condition that can be diagnosed prenatally (Richardson & Yonekawa, 2018).

Pathophysiology. Normally, ADH secretion is triggered by changes in osmolality detected by supraoptic and paraventricular osmosensors in the brain. Increased osmolality stimulates the posterior pituitary to release ADH, which in turn increases the permeability of the renal collecting tubules to water, reducing

urinary water loss. Damage to the osmosensors, the posterior pituitary gland, or the hypothalamic–hypophyseal axis results in a deficiency of ADH and increased urinary free water loss.

Clinical Manifestations. Neonates with DI may suck vigorously during feeding but vomit immediately afterward, resulting in poor growth. **Emergency Alert: Urine output is high, in excess of 5 mL/kg/hour, with low specific gravity (<1.010). Irritability and fever may accompany evidence of dehydration (poor skin turgor, depressed anterior fontanel, sunken eyes, mottled skin, weak pulses, low blood pressure, and constipation).**

Diagnosis. Serum electrolytes, osmolality, and plasma ADH levels are the primary laboratory tests used to diagnose DI. Plasma ADH is normally elevated in the newborn following delivery, playing a role in the low urine output that is typical on the first day of life. In neonates with DI, hypernatremia may result in levels as high as 180 mEq/L with elevated serum osmolality. Urinalysis reveals inappropriately dilute urine (low urine osmolality and low specific gravity). MRI is used to visualize the pituitary gland and stalk to delineate the possible cause of DI.

Management. DI in neonates requires very careful fluid management. Severe dehydration and hypernatremia are corrected primarily with intravenous fluids. Insensible water losses should be minimized. **Quality and Safety: Serum electrolytes and osmolality, blood glucose, accurate intake and output, and the evidence of dehydration (weight loss, blood pressure, pulses, skin turgor, etc.) should be closely monitored during treatment.** **Emergency Alert: Infants with severe hypernatremia must be observed for possible seizure activity.** Although it is expected that serum sodium will decline, very rapid shifts in serum sodium should be avoided. During therapy to correct serum sodium, the infant's neurologic status must be monitored closely for signs and symptoms of cerebral edema. **Quality and Safety: Hyperglycemia must be avoided as this may lead to glycosuria and exaggerate the diuresis.** If possible, DI in the neonate should be managed with fluid therapy alone, preferably breast milk or formula with a whey-to-casein ratio of 60 to 40, supplemented with free water if necessary (Srivatsa, Majzoub, & Kappy, 2014). If it is not possible to manage DI with fluids alone, the agent of choice for pharmacologic treatment is desmopressin (DDAVP), a long-acting synthetic analogue of pituitary ADH. Intranasal DDAVP can be diluted with normal saline for administration to the neonate. Subcutaneous and oral formulations of DDAVP are also available, as well as short-acting intravenous aqueous pitressin for emergency treatment of severe dehydration. **Emergency Alert: Caution must be observed when using vasopressin and high fluid intake to manage DI in the neonate because this combination can result in severe hyponatremia** (Srivatsa et al., 2014).

Syndrome of Inappropriate Antidiuretic Hormone

Syndrome of inappropriate antidiuretic hormone (SIADH) is an impairment of free water clearance associated with inappropriately raised secretion of ADH. SIADH is believed to be associated with CNS infection and injury (birth asphyxia, intracranial hemorrhage, meningitis), pain, and maternal substance abuse (Modi, 2012).

Pathophysiology. An uncontrolled release of ADH can occur in sick preterm and term infants, resulting in renal free water retention that is inappropriate to the level of serum osmolality. The infant becomes hyponatremic, not because of true sodium depletion, but because of a dilutional effect from the fluid that is retained. ADH levels can become elevated in infants born after fetal distress, or those with severe pulmonary disease, undergoing surgery, or experiencing pain. Raised ADH levels are common in acutely ill neonates (Modi, 2012).

Clinical Manifestations. Signs and symptoms of SIADH are oliguria, hyponatremia, low serum osmolality (<275 mOsm/L), weight gain, and edema. Patients with SIADH are euvolemic or hypervolemic.

Diagnosis. The diagnosis of SIADH should be made only when hyponatremia exists with normovolemia, normal blood pressure, normal renal and cardiac function, evidence of continuing sodium excretion, and urine that is not maximally dilute (Modi, 2012). True SIADH fulfilling all diagnostic criteria is probably uncommon in the neonate. Apparent SIADH may be due to hypovolemia-induced baroreceptor-driven ADH secretion, a normal response to reduced blood volume in the sick neonate (Modi, 2012).

Collaborative Management. Fluid restriction, with close monitoring of intake, output, serum electrolytes, blood glucose, accurate daily weights, evidence of increasing edema, and measures of hydration, are the essentials of management. It can be difficult to restrict fluids because infants receive all of their nutrition in liquid form. Diuretics are sometimes used to promote free water excretion. Comparison of intake and output is important. **Quality and Safety: A careful neurologic assessment should be performed, noting changes in relation to fluid or sodium balance.**

THYROID GLAND

The thyroid gland is a butterfly-shaped structure made up of two lateral lobes connected by a thin band of tissue called the isthmus. Composed of densely packed follicular cells containing colloid, the thyroid gland also contains parafollicular cells (C-cells) that produce the calcium-lowering hormone calcitonin.

The thyroid hormones thyroxine (T_4) and triiodothyronine (T_3) are produced from the amino acid tyrosine. Essential to this process is the trapping and storage of iodide, a trace element required for thyroid hormone synthesis. Thyroglobulin (Tg), a thyroid hormone precursor, is synthesized in the follicular cell. Iodine is taken up by the Tg molecule, incorporated into its tyrosine residues, and returned to the colloid, where a coupling reaction takes place. This step, called organification, is catalyzed by the enzyme thyroid peroxidase (TPO). The coupling of two tyrosine residues produces T_4, whereas the coupling of diiodotyrosine (DIT) with monoiodotyrosine (MIT) produces T_3. These are stored in the follicular lumens until TSH stimulates their release into the circulation.

The thyroid gland produces mostly T_4, which serves as a storage pool for T_3. T_3 is the most biologically active thyroid hormone, with greater affinity for the thyroid receptor. Circulating T_4 is metabolized by outer ring 5' monodeiodination to T_3 in the peripheral tissues. Inner ring 5' monodeiodination of T_4 produces reverse T_3 (rT_3), an inactive metabolite. T_4 and T_3 circulate in plasma bound to thyroid-binding globulin (TBG), leaving just a small fraction in equilibrium as free hormone. It is possible for TBG, which is synthesized in the liver, to be deficient even though the free hormone levels are normal. It is the free hormone that is available to the tissues, with the bound hormone acting as a circulating reservoir. The concentration of free hormone determines the individual's metabolic state.

The hypothalamic–pituitary–thyroid (HPT) axis controls thyroid hormone secretion (Figure 10.1). The hypothalamus synthesizes thyrotropin, stimulating release of TSH from the anterior pituitary. In turn, TSH stimulates uptake of iodine by the thyroid, thyroid hormone synthesis and release, and increased size and

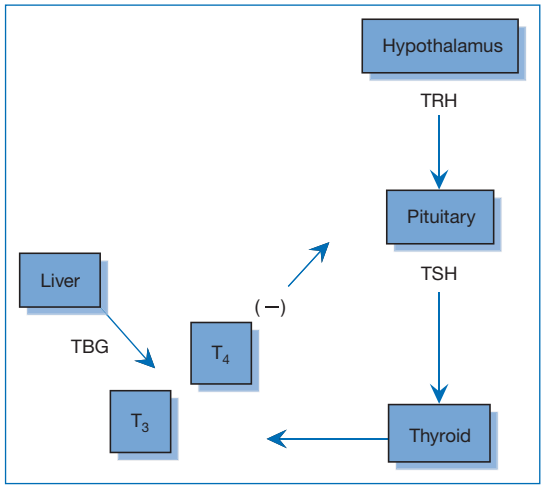

FIGURE 10.1 The hypothalamic–pituitary–thyroid (HPT) axis. Thyroid hormone levels are regulated by a system of feedback inhibition operating along the HPT axis. The hypothalamus secretes thyrotropin-releasing hormone (TRH), which stimulates the pituitary to secrete thyroid-stimulating hormone (TSH). TSH, in turn, stimulates the thyroid gland to produce and secrete thyroid hormones (T_4 and T_3) into the circulation, which circulate bound to thyroid-binding globulin (TBG) synthesized by the liver. Once levels of T_4 and T_3 are adequate, further production of TSH is suppressed.

vascularity of the thyroid gland itself. The feedback loop is responsive to changes in free hormone concentration, and TSH secretion adjusts accordingly.

FETAL AND NEONATAL THYROID DEVELOPMENT

The thyroid gland is the first endocrine organ to develop in the human embryo. Concurrent with development of the fetal thyroid are growth and maturation of the hypothalamus and pituitary glands, which are required for thyroid function. At about 10 to 12 weeks gestation, the hypothalamus begins synthesizing thyrotropin-releasing hormone (TRH), the pituitary gland begins secreting TSH, and thyroid-binding globulin (TBG) is detectable in fetal serum. Maternal thyroxine is measurable in amniotic fluid before the onset of fetal thyroid function. Before 20 weeks gestation, transplacental passage of maternal T_4 largely provides for fetal thyroidal needs and is critical for normal development. Maternal hypothyroidism during early gestation can impair CNS development in the fetus. By the start of the second trimester, however, the fetal contribution to circulating thyroid hormones is significant. The capacity of the fetal thyroid gland to trap and store iodide and synthesize thyroid hormones begins at about 11 weeks gestation, but hormone production is limited until 18 to 20 weeks, when iodine uptake increases markedly. The only source of iodide for the fetus is transplacental passage from the maternal circulation and placenta.

As pregnancy progresses, the placenta becomes less permeable to maternal thyroid hormone. Permeability is likely to be highest during the first trimester because thyroid hormone is critical to fetal neurodevelopment, and no other source is available to the fetus during this period. The fetal HPT axis develops from mid-gestation through 4 weeks post birth. In infants born before term, maturation of the HPT axis is disrupted (Simpser & Rapaport, 2010). In the last trimester, the fetus is less dependent on maternally derived thyroid hormone. Although thyroid hormone is required for CNS maturation, it is not needed for metabolism, growth, or generation of heat. An excess of bioactive T_3 could be harmful to fetal development. For this reason, the concentration of T_3 is tightly controlled in the tissues (van Wassenaer & Kok, 2004). This is accomplished by preferential conversion of excess fetal T_4 to the bioinactive reverse T_3 by type III deiodinase. In the event of T_4 deficiency, as in fetal hypothyroidism, T_4 is shunted to the brain where it is deiodinated to T_3 to provide a critical source of intracellular T_3 to the developing brain.

Birth represents a temporary state of hyperthyroidism for the newborn. In response to sudden exposure to a cold environment, the pituitary releases a surge of TSH that peaks at 70 to 100 mU/mL at 30 minutes after birth. This cold-stimulated TSH surge provokes rises in serum T_4, T_3, and free T_4, all of which peak at about 48 hours. T_4 increases in most infants to a level of 6.5 mcg/dL or higher. The rise in T_4 causes the TSH to decline to 20 mU/mL or less (the cutoff used in most screening programs for congenital hypothyroidism [CH]) because of feedback inhibition. Free and total T_4 and T_3 gradually decrease over the next 1 to 2 months.

CONGENITAL HYPOTHYROIDISM

CH is a deficiency of thyroid function present at the time of birth. With an incidence of 1 in 2,000 to 4,000 births (Rastogi & LaFranchi, 2010), it is the most common congenital endocrine disorder (Polak, Refetoff, Szinnai, & Van Vliet, 2017). CH is classified as either permanent or transient, depending on the underlying etiology. Early diagnosis and appropriate treatment are essential to prevent permanent neurologic damage. Because most affected infants are asymptomatic at birth, neonatal screening for hypothyroidism is now mandated so infants with CH are promptly identified and treated.

Causes of Congenital Hypothyroidism

Thyroid Dysgenesis. The most common cause (85%) of permanent CH is thyroid dysgenesis, which includes thyroidal ectopy, hypoplasia, and complete thyroid agenesis. The severity of thyroid dysfunction is variable, depending on the amount of functional thyroid tissue present. Thyroidal ectopy accounts for two-thirds of neonates with thyroid dysgenesis. Ectopic thyroid tissue (lingual, sublingual, subhyoid) provides adequate amounts of thyroid hormone in some infants. Occasionally, ectopias are associated with thyroglossal duct cysts. Most of these infants have a thyroid remnant, usually found midline at the base of the tongue, as a result of failure of the gland to descend normally during embryologic development.

Thyroid dysgenesis occurs in 1 in 4,000 live births; however, the incidence in Black infants is 1 in 32,000 live births and in Hispanic infants, 1 in 2,000. The disorder has a female to male ratio of 2 to 1. Only 3% of thyroid dysgenesis is due to mutations in the homeobox genes that control thyroid differentiation *(TTF-2*, *NKX2.1*, *NKX2.5*, or *PAX-8*; Tenore & Driul, 2009). Trisomy 21 or Down syndrome is associated with an increased prevalence of thyroid dysgenesis, and extrathyroidal abnormalities (cardiac, gastrointestinal, CNS, and eyes) are also more common. No serum Tg is measurable in thyroid agenesis, distinguishing it from functional thyroid tissue, which is associated with measurable serum Tg concentrations.

Thyroid Dyshormonogenesis. About 10% to 20% of infants with CH have inborn defects of thyroid hormone metabolism. Mutations in genes coding for proteins involved in thyroid hormone synthesis, secretion, or transport result in failure of one of the steps in this process, leading to thyroid insufficiency. These biochemical defects are usually inherited as autosomal recessive

traits and include TSH hormone resistance, iodide organification defects, iodide transport defects, iodotyrosine deiodinase defects, and thyroglobulin deficiency. Deficient activity of the enzyme TPO is one of the most common disorders of thyroid synthesis caused by mutations of *THOX1* or *THOX2* (Kim, Nandi-Munshi, & DiBlasi, 2018). Although dyshormonogenesis eventually results in a compensatory goiter, it is not typically apparent during the neonatal period.

Thyroid-Binding Globulin Deficiency. Infants born with congenital thyroid-binding globulin (TBG) deficiency have low TBG and total T_4 but normal TSH concentrations and are normal with respect to thyroid function. Familial congenital TBG deficiency, transmitted as an X-linked trait, occurs in 1 in 9,000 newborns (Simpser & Rapaport, 2010). The defect can be complete or partial and is frequently an incidental finding on neonatal screening. A TBG level can be measured to confirm the diagnosis for the purpose of parental counseling, but no treatment is recommended.

Hypothalamic–Pituitary Hypothyroidism. Between 5% and 10% of infants with CH can be accounted for by what is called secondary–tertiary or central hypothyroidism. A deficiency of hypothalamic TRH or pituitary TSH can occur as a consequence of a developmental defect of the pituitary or hypothalamus. Central hypothyroidism is generally associated with other anomalies of the midbrain (such as absence of the septum pellucidum or other midline defects), hypopituitarism, pituitary stalk interruption, or empty sella syndrome, all of which lead to typical laboratory findings of low serum T_4 and low or inappropriately normal serum TSH.

Thyroid Hormone Resistance. Increasing numbers of patients are being found with resistance to the actions of endogenous and exogenous T_4 and triiodothyronine (T_3), a form of "peripheral hypothyroidism." At least 90% of these cases are caused by a mutation in the genes encoding for thyroid hormone receptor-beta (Rastogi & LaFranchi, 2010). Most patients have goiter, and levels of T_4, T_3, free T_4, and free T_3 are elevated. These findings have often led to the erroneous diagnosis of Graves' disease, although most affected patients are clinically euthyroid. The unresponsiveness to thyroid hormone may vary among tissues.

Clinical Manifestations of Congenital Hypothyroidism

Few neonates are diagnosed with CH solely on clinical grounds. Signs and symptoms of CH can be slow to develop owing to persistence of maternal thyroid hormone. When present, signs and symptoms of CH in the neonate are subtle and nonspecific; thus, they are not immediately linked with hypothyroidism. **Quality and Safety: Early diagnosis is critical, however, to ensure prompt treatment that will reduce the risk for mental retardation.** The signs and symptoms of hypothyroidism in the neonate reflect the wide-ranging actions of thyroid hormones on metabolism, intestinal motility, cardiac function, temperature regulation, neurologic function, and skeletal maturation (Box 10.1). The possibility of CH must be considered in infants presenting with birth weight in excess of the 90th percentile, prolonged jaundice, hypothermia, and cold mottled skin, an enlarged (>1 cm) posterior fontanel, umbilical hernia, and failure to feed well (Rastogi & LaFranchi, 2010).

Other features traditionally associated with hypothyroidism (macroglossia, dry skin, lethargy, hypotonia, hoarse cry, coarse hair, and constipation) evolve over the first weeks of life. A palpable, enlarged thyroid gland (also called a goiter) can be associated with impaired thyroid hormone synthesis and hypothyroidism. Hyperplasia of the thyroid gland results from hypersecretion of TSH in response to low T_3 and T_4 levels. Infants with suspected central hypothyroidism may present with midline or cranial defects or other signs of pituitary deficiency. Central hypothyroidism should be suspected in infants presenting with septo-optic dysplasia, hypoglycemia, micropenis, or cleft lip/palate.

Box 10.1

SIGNS AND SYMPTOMS OF HYPOTHYROIDISM IN THE NEONATE

- Birth weight >4 kg, gestation longer than 42 weeks
- Large, open posterior fontanel (>1 cm)
- Umbilical hernia
- Abdominal distension
- Poor feeding
- Hypothermia, cool extremities
- Prolonged jaundice
- Bradycardia
- Poor muscle tone
- Mottled skin
- Delayed skeletal maturation

Diagnosis of Congenital Hypothyroidism

Neonatal Screening. Because even severe CH can be clinically silent, universal newborn screening for CH is widely practiced. Routine screening of all newborn infants for CH has greatly improved early detection and treatment of the disorder, preventing much of the mental retardation that was previously associated with CH. Newborn screening was first introduced as a public health program in the United States in the early 1960s, and has expanded to other countries around the world, with different testing menus in each country. The conditions included in the newborn screening programs around the world vary greatly, based on the legal requirements for screening programs, prevalence of certain diseases within a population, political pressure, and availability of resources for both testing and follow-up of identified patients.

The incidence of CH, as detected through newborn screening, is approximately 1 per 3,000 to 4,000. Screening all newborns for CH is mandated in all U.S. states and throughout Canada. Recent increases in the incidence of CH reported by some screening programs could be the result of increased detection of mild hypothyroidism and preterm infants with delayed TSH rise (Mitchell, Hsu, Sahai, & Massachusetts Pediatric Endocrine Workgroup, 2011).

Some screening programs in North America measure the TSH directly from blood samples collected on filter paper. Other programs initially measure T_4 on all specimens, followed by TSH measurement only if T_4 is low. Owing to the physiologic surge in TSH in the first hours of life as the newborn adapts to the extrauterine environment, the screening specimen must be collected when the infant is at least 24 hours of age, and preferably between 2 and 4 days of age. If blood is collected earlier, particularly in the first 3 hours of life, a false positive result can occur. In those instances, a repeat specimen must be collected within the first 7 days of life, regardless of prior test results. Protein intake is not required prior to screening for CH.

False negatives can also occur with screening. When only T_4 testing is done, as many as 8% of infants with central CH can be missed (Kim et al., 2018). Their initial T_4 levels are in the normal

range (Kim et al., 2018). A similar problem can occur with infants who have hypothyroxinemia with delayed TSH elevation and those with residual thyroid tissue (such as an ectopic thyroid gland), because their initial T_4 levels are also in the normal range. All of these infants would be detected by repeat screening at 2 to 6 weeks of age.

Certain infants are at risk for a missed or delayed diagnosis, including those born at home, those who are extremely ill in the neonatal period, and those who are transferred between hospitals at an early age. Screening errors, including incorrect specimen collection, or improper storage and transport can result in a false negative test. Thyroid medications taken by the mother during pregnancy can also produce false negative results. Blood transfusions can alter test results. Preservatives (EDTA or citrate) in blood-collection containers can result in false negative or false positive screening results.

When a low T_4 and elevated TSH level (>40 mU/L) are encountered, the neonate should be presumed to have primary hypothyroidism until proven otherwise. A thorough examination for signs and symptoms of CH is indicated, along with confirmatory serum testing. Treatment with L-thyroxine should be initiated while awaiting the results of further testing.

Laboratory Testing. Low serum total and free T_4 and T_3, along with elevated TSH levels, confirm CH in the neonate. Permanent congenital CH is highly likely in a full-term neonate with a serum T_4 less than 6 mcg/dL and a serum TSH greater than 50 mU/L. A normal T_4 (e.g., >10 mcg/dL) in combination with elevated TSH suggests that the infant has enough functional thyroid tissue to respond to excess TSH stimulation, the pattern seen in a subgroup of infants with compensated or subclinical hypothyroidism. Age-related reference norms, for both gestational age and hours of age, should be used when interpreting all thyroid test results. If maternal antibody-mediated hypothyroidism is suspected, maternal antithyroid (TSH receptor–blocking, TRBAb) antibody testing should be done. Other thyroid autoantibodies that can produce hypothyroidism include thyroglobulin (TGAb) and thyroid peroxidase antibodies (TPOAb). TBG levels can be measured to rule out TBG deficiency. Thyroglobulin levels in infants with possible CH can help to differentiate between thyroid agenesis and dyshormonogenesis, as an adjunct to thyroid imaging. Genetic studies have already helped to identify the etiology of CH in some infants.

Imaging Studies. Infants with biochemical evidence of CH usually undergo scintigraphy with iodine-123 (^{123}I) or pertechnetate ($^{99m}TcO_4$), which is trapped by the thyroid gland and like iodine (Polak et al., 2017) aids in detection of an ectopic (lingual or sublingual) or missing gland. A normal or enlarged gland suggests a defect in thyroxine synthesis as the source of CH. Thyroid ultrasound can also be useful initially to demonstrate presence or absence of a gland. Lateral radiographs of the knee and foot reveal bone age, indicating the degree of intrauterine hypothyroidism experienced by the fetus. Ossification of the distal femoral epiphysis usually appears at 36 weeks gestation; its absence in a term or post term infant suggests delayed bone maturation from long-standing hypothyroidism.

Management of Hypothyroidism

Early, adequate treatment of permanent CH is critical for optimal neurologic development. The goal of hormone replacement therapy is to rapidly normalize the infant's serum T_4 level and maintain it in the upper half of the normal range, which should result in a TSH of 0.5 to 4 mU/L (Kim et al., 2018). The agent of choice is sodium-L-thyroxine (NaT_4) because it is substantially converted to T_3 within the brain. Tablets are crushed and given in a small amount of liquid. One method is to instruct parents to crush the tablet and place it on the baby's tongue just before feeding (Polak et al., 2017). The tablet should not be diluted in the entire volume of the baby's bottle because if the bottle is not finished, the baby will not receive the full dose needed. Parents should be counseled about the importance of consistent administration of the medication, and instructed on actions to take if a dose is missed or the infant vomits after a dose is given.

Infants receiving thyroid replacement therapy must be monitored closely for adequacy of treatment and evidence of thyrotoxicosis (irritability, tachycardia, poor weight gain). Serum T_4 should normalize in 1 to 2 weeks; serum TSH can take longer to normalize.

TRANSIENT DISORDERS OF THYROID FUNCTION

Transient Hypothyroxinemia of Prematurity

Preterm infants have the same incidence of permanent CH as full-term infants (Srinivasan, Harigopal, Turner, & Cheetham, 2012). In addition, about 50% of infants born at less than 30 weeks gestation exhibit transiently low thyroxine levels when compared with their full-term counterparts. This relative hypothyroxinemia is primarily a function of HPT axis immaturity, a physiologically normal stage of thyroid system development. However, many other factors influence thyroid function, particularly in the extremely preterm infant (Hyman, Novoa, & Holzman, 2011). The abrupt cessation of maternal T_4 supply, occurring at the time of birth when demand for thyroid hormone is high, contributes to low thyroid hormone levels. Other factors include immature ability to concentrate iodine and to synthesize and iodinate thyroglobulin. Preterm infants may also suffer from insufficient iodine intake during the early weeks after birth before full enteral feeding is established. In addition, iodine excess related to the use of iodine-containing antiseptics and radiopaque agents can interfere with thyroid function by blocking thyroid hormone release from the thyroid gland.

Pathophysiology. The postnatal TSH surge of the preterm infant is similar, yet quantitatively lower, than that of the more mature infant. Likewise, the corresponding rise in T_4 that occurs in preterm infants is blunted in comparison to term infants. It takes approximately 4 to 8 weeks, depending on the gestational age at birth, for normal term hormone levels to be reached. The more premature the infant, the more severe the hypothyroxinemia is. Infants with transiently low thyroxine need follow-up testing to ensure that the low T_4 levels rise into the normal range over time.

Extremely preterm infants (24–27 weeks gestation) are at an even greater disadvantage, having a distinct and more ineffective pattern of postnatal thyroid function. The TSH surge of these very immature infants is significantly attenuated, and TSH levels continue to fall after birth to less than cord blood values by 7 hours of age. Such very low TSH levels fail to stimulate a postnatal rise in T_4 at all. T_4 levels in extremely immature infants remain quite low after birth and are even slightly lower than cord blood values at 24 hours of age.

Clinical Manifestations. Hypothyroxinemia of prematurity is a subtle condition with no overt signs or symptoms of hypothyroidism. Many classic signs and symptoms of hypothyroidism are common clinical findings in the preterm infant (slow intestinal motility, distension, prolonged jaundice, low muscle tone, mottled skin, etc.). **Quality and Safety: Thyroid hormones are critical to brain development, so a prolonged low thyroxine level while the brain is still undeveloped could be a factor in poor neurocognitive outcomes in these infants.**

Diagnosis. Hypothyroxinemia of prematurity is identified by routine newborn screening. T_4 and free T_4 are low, but TSH is not elevated above the cutoff of 20 mU/L. This is the critical difference between transient hypothyroxinemia of prematurity and CH. A repeat test is conducted after several weeks to recheck T_4 and monitor for a possible delayed rise in TSH.

Management. The bothersome fact about hypothyroxinemia of prematurity is that it is associated with higher mortality and neurodevelopmental deficits, yet cumulative evidence to date has not been able to demonstrate clear benefits of routinely supplementing these infants with thyroxine during early life. It has been suggested that using a continuous dose of 4 mcg/kg/day, rather than a single daily supplement, would be a more physiologic way to raise thyroxine levels and maintain biologic euthyroidism in very low gestational age infants (La Gamma et al., 2009). However, long-term studies to show the neurocognitive benefit of this approach are lacking. A recent *Cochrane Database of Systematic Reviews* did not support the use of prophylactic thyroid hormones in preterm infants to reduce neonatal mortality and neonatal morbidity or improve neurodevelopmental outcomes (Osborn & Hunt, 2007). The exception is the infant with an elevated TSH level; these infants require treatment. Thyroid function tests should be followed carefully in preterm infants at risk for hypothyroxinemia, and treatment should be instituted promptly if indicated by elevated TSH. It is a good idea to flag or highlight the low thyroid results from the initial newborn screen to ensure that repeat thyroid testing is not overlooked.

However, we should not assume that just because studies to date have not been able to demonstrate the benefits of treating hypothyroxinemia of prematurity this condition is not significant. The persisting neurodevelopmental deficits in extremely low gestational age neonates could be, in part, related to their thyroid status during critical periods of CNS development (La Gamma & Paneth, 2012).

Nonthyroidal Illness

In some ill preterm infants, T_4 is preferentially converted to rT_3 instead of T_3, possibly as an adaptive response to lower the metabolic rate during times of severe illness. The outcome is low serum concentrations of both T_4 and T_3. Reverse T_3 is elevated and TSH is normal. This condition, also known as "low T_3 syndrome" or "euthyroid sick syndrome," occurs in infants who have immature lungs or infections, because the cytokines produced in response to illness or inflammation are believed to inhibit thyroid function, metabolism, or action (van Wassenaer & Kok, 2004). The low T_4 from nonthyroidal illness reverses spontaneously when the infant's condition improves. No treatment is required. Similar effects are seen in infants who are receiving dopamine or glucocorticoids, both of which can lower serum T_4 concentrations.

Transient Primary Hypothyroidism

Hypothyroidism is defined as transient when a low T_4 and elevated TSH in apparently healthy full-term infants revert to normal spontaneously or after several months of thyroxine supplementation. About 5% to 10% of the infants identified by newborn screening programs as having CH eventually are recognized as having a transient condition. Initial management is the same as for CH.

Transplacental Passage of Drugs or Antibodies

Transient hypothyroidism in the newborn can be precipitated by transplacental passage of antithyroid agents taken during pregnancy for the treatment of maternal Graves' disease. Medications such as propylthiouracil (PTU), methimazole, radioiodine, and amiodarone can inhibit fetal thyroid production. A similar inhibitory effect can occur if the fetus is exposed to excess iodine in utero. If the mother has a history of autoimmune thyroid disease, maternal TSH receptor–blocking antibodies (TRBAb, also termed thyrotropin binding inhibitor immunoglobulin, or TBII) readily cross the placenta and block the fetal thyroid, producing hypothyroidism. These TRBAbs can persist in the infant's circulation for 2 to 3 months after birth before they are completely metabolized and disappear. However, it can be difficult to predict the effects of these antibodies because some mothers will simultaneously produce TSH-receptor stimulating antibodies that will offset the effects of the TRBAbs.

Clinical Manifestations. Like CH, transient hypothyroidism is usually asymptomatic in the newborn. If present, the signs and symptoms are the same as for CH. Transient hypothyroidism caused by antithyroid drugs (goitrogens) can cause a goiter in the neonate. Iodine deficiency or excess has a similar effect.

Diagnosis. Transient hypothyroidism is typically detected by routine neonatal screening or is based on maternal history. The neonate displays the thyroid profile of low T_4 and elevated TSH that is characteristic of hypothyroidism. When the maternal history is positive for autoimmune thyroid disease, thyroid stimulating hormone antibodies (TRSAb) and TRSAb levels (as indicated) are also obtained for baseline purposes. Thyroid imaging tests may also be conducted.

Management. Transient hypothyroidism caused by maternal antithyroid medication will resolve spontaneously when the medication is cleared from the infant's circulation, usually within a day or two after birth. The infant's serum T_4 and TSH should be monitored to ensure that they return to normal. Supplementation with L-thyroxine is not usually necessary. Transplacentally acquired TSH receptor–blocking antibodies can be slow to degrade completely; therefore, most infants will require supplementation for several months. TRBAb levels in the infant can be monitored to determine when to discontinue therapy. Breastfeeding is not contraindicated in neonates whose mothers continue their antithyroid medication in the postpartum period, as very little passes into the breast milk.

Hyperthyroidism (Neonatal Graves' Disease)

Pathophysiology. The transient condition neonatal Graves' disease occurs in infants born to mothers with active or inactive Graves' disease, to those who have undergone thyroidectomy or radioiodine ablation of the thyroid gland, and to women taking antithyroid drugs. Maternal TRSAbs cross the placenta readily and stimulate the fetal thyroid gland, causing an overproduction of thyroid hormone and, in some cases, development of a goiter. Usually the higher the TRSAb level in the mother, the more severely affected the infant will be. Hyperthyroidism in the neonate is typically transient, lasting approximately 3 to 12 weeks. The clinical course varies depending on characteristics of the mother's disease and treatment. The onset of hyperthyroidism may be delayed for a week or longer in neonates whose mothers produce not only TRSAb but TSH receptor–blocking antibodies as well. Similarly, if the mother took antithyroid medication during pregnancy, the neonate might not exhibit evidence of hyperthyroidism for several days until the drugs are metabolized (and, in fact, some infants are hypothyroid during that time). Occasionally, the hyperthyroidism persists beyond the expected recovery period and becomes true, permanent Graves' disease.

Clinical Manifestations. Neonates may be born preterm, often with evidence of intrauterine growth restriction. Common clinical signs of thyrotoxicosis include tachycardia, arrhythmias, hypertension,

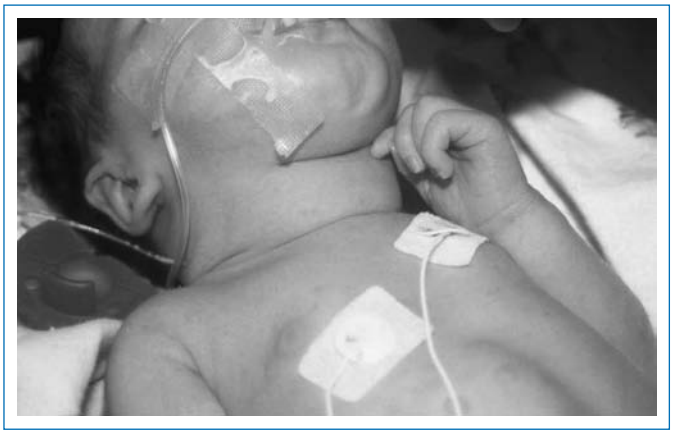

FIGURE 10.2 Newborn infant presenting at birth with goiter.

tachypnea, poor feeding, vomiting, sweating, hyperthermia, flushing, diarrhea, restlessness, tremors, irritability, and hyperalertness. In severe cases of untreated maternal Graves' disease, advanced bone age, craniosynostosis, and microcephaly are evident in both the fetus and newborn. The infant should be examined for a goiter, which can be very small or large enough to compress the trachea and cause respiratory distress in the newborn. A goiter is a symmetrical, smooth enlargement of the gland and can be recognized as a swelling in the anterior neck of the neonate (Figure 10.2). To examine the neonate for goiter, place the infant supine and elevate the trunk while allowing the head to fall back gently (Escobar, Viswanathan, & Witchel, 2018). It is important to appreciate that a goiter can increase in size during the early neonatal period.

Diagnosis. Serum T_4, free T_4, and T_3 are elevated, and serum TSH is low, all relative to age-appropriate norms. A TRSAb titer in the neonate will give an indication of the expected severity of the disease course. **Emergency Alert: Infants at risk (e.g., high maternal titer of TRSAb) for severe thyrotoxicosis require frequent monitoring of free T_4 and TSH.** A good maternal history is essential (e.g., history of radioablation therapy, antithyroid drugs taken during pregnancy and when they were taken, and maternal symptoms, if any).

Management. The mainstays of treatment of hyperthyroidism in the neonate are iodine, antithyroid medication, sedation, and beta-adrenergic blockers, if needed. Treatment is tailored to the severity of the infant's symptoms. Lugol's iodine solution (potassium iodide), given in a single drop three times daily, acutely inhibits the release of thyroxine from the thyroid gland. Other preparations include iodine-based contrast agents (ipodate), PTU, and methimazole. Propranolol can be used to manage cardiovascular symptoms. The infant's serum T_4 must be followed closely during treatment for possible iatrogenic hypothyroidism. TRSAb levels are also followed to monitor the infant's recovery and aid in determining the appropriate time for weaning antithyroid medication.

ADRENAL GLAND

The highly vascular adrenal glands are located at the superior poles of the kidneys. Each gland is composed of two distinct, independently functioning organs: the outer cortex, which produces steroid hormones (mineralocorticoids, glucocorticoids, and androgens), and the inner medulla, which produces catecholamines. Adrenal steroid production and regulation require a functional HPA axis. Cortisol is also released in response to stress, hypoglycemia, surgery, extreme heat or cold, hypoxia, infection, or injury.

Aldosterone, the most important mineralocorticoid, regulates renal sodium and water retention and potassium excretion. Aldosterone influences not only electrolyte balance but blood pressure and intravascular volume as well. Aldosterone is regulated by the plasma renin-angiotensin system.

Adrenal androgens include dehydroepiandrosterone (DHEA), DHEA sulfate, and androstenedione and are regulated by ACTH. These steroids have minimal androgenic activity but are converted in the peripheral tissues to two more potent androgens, testosterone and dihydrotestosterone (DHT), required for normal sexual differentiation.

FETAL ADRENAL GLAND

The fetal adrenal gland is evident from 6 to 8 weeks gestation and rapidly increases in size. Fetal cortisol is secreted at 8 weeks gestation. Early in gestation, the fetal adrenal cortex differentiates into three regions: an inner prominent fetal zone, an outer definitive zone, and a transitional zone. After birth, the fetal zone involutes and the definitive zone is transformed into the mature gland. Cortisol maintains intrauterine homeostasis and influences the development of a wide variety of fetal tissues. Cortisol is essential for prenatal maturation of organ systems, including lungs, GI tract, liver, and the CNS, which are vital for neonatal survival.

The fetal adrenal gland and the placenta are an integrated endocrine system known as the fetoplacental unit. The fetal zone of the developing adrenal gland produces DHEA and DHEA sulfate, precursors for placental estrogen, which is critical to maintenance of the pregnancy and fetal well-being. In turn, the placenta regulates fetal exposure to maternal cortisol by oxidizing cortisol to the biologically inactive cortisone, protecting the fetus from excessive cortisol levels. The placenta also releases corticotropin-releasing hormone (CRH), which heightens activity of the fetal HPA axis and stimulates fetal cortisol production. All of this contributes to the prenatal cortisol surge that prepares the fetus for the stress of birth and adaptation to the extrauterine environment.

NEONATAL ADRENOCORTICAL FUNCTION

Plasma cortisol levels are elevated at the time of birth but decline in the first few days of life. In term infants, a nadir is seen on day 4 of life. Likewise, levels of cortisol precursors such as 17-hydroxyprogesterone (17-OHP) are high at birth but decrease to normal neonatal levels by 12 to 24 hours of age. Cortisol is regulated by pituitary ACTH, which in turn is controlled by hypothalamic CRH via a negative feedback loop. Cortisol in the newborn plays a key role in response to stress and illness, and is important in the maintenance of blood pressure (Ng, 2011).

Aldosterone and plasma renin activity (PRA) are elevated in neonates compared with values for older infants, allowing for positive sodium balance until the kidneys fully mature. The hyponatremia and urinary sodium losses often seen in preterm infants during the early postnatal weeks are due to a relative mineralocorticoid deficiency as a consequence of immaturity of both the kidneys and the adrenal glands.

ADRENAL DISORDERS IN THE NEONATE

Transient Adrenocortical Insufficiency of Prematurity

A limited ability of the adrenal glands to maintain cortisol homeostasis in the early days of life has been observed in some preterm newborns. Manifestations are a low serum cortisol,

normal or exaggerated pituitary response, and good recovery of adrenal function by day 14 of life (Ng, 2011). A proportion of very-low-birth-weight infants with inotrope and volume-resistant hypotension show an inadequate adrenal response to stress in the immediate postnatal period (Ng, 2011). Whether a relative adrenal insufficiency contributes to hemodynamic instability and hypotension in critically ill infants is still under debate (Fechner, 2018).

Adrenal Hemorrhage

Adrenal hemorrhage in the neonate can be precipitated by traumatic delivery, breech presentation, macrosomia, or disseminated intravascular coagulation. The large size and vascularity of the fetal adrenal gland predisposes the gland to injury and rupture during the birth process. Although it is often asymptomatic, classic findings include jaundice, pallor, or a flank mass on either side (although hemorrhage is more common on the right), with discoloration and purpura of the overlying skin and discoloration of the scrotum (Mutlu, Karagüzel, Aslan, Cansu, & Ökten, 2011). In severe cases, the infant may exhibit signs of adrenal insufficiency. Small hemorrhages can be initially undetected, but eventually manifest in anemia and persistent jaundice (Askenazi, Selewski, Willig, & Warady, 2018). Adrenal hemorrhage can be visualized on ultrasound and usually resolves in 4 to 16 weeks (Mutlu et al., 2011).

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH) is a spectrum of autosomal recessive disorders resulting from a deficiency of one of the five enzymes required to synthesize cortisol from cholesterol in the adrenal cortex. Each enzyme is encoded by its own gene, and mutations in the 21-hydroxylase (21-OHD) gene, *CYP21A2*, are the most frequent. To date, 127 different mutations of *CYP2A12* have been described, ranging from complete loss of enzyme function to partial enzyme activity (Witchell & Azziz, 2011). The severity of the disease correlates with *CYP21A2* allelic variation (Speiser et al., 2010). 21-OHD deficiency accounts for 95% of CAH and is the most common cause of ambiguous genitalia of the neonate.

Pathophysiology. A lack of 21-OHD prevents conversion of progesterone to its two end products: cortisol and aldosterone (Figure 10.3). By reduced negative feedback regulation, the absence of cortisol causes oversecretion of ACTH, which chronically stimulates the adrenal cortex, resulting in hyperplasia of the gland. The precursor steroids proximal to the blocked step accumulate and are shunted into other metabolic pathways such as androgen biosynthesis. In a female fetus, these superfluous yet potent systemic androgens cause virilization of the developing external genitalia. Also, the effects of this androgen exposure on the developing CNS may be important. Internal reproductive organs (ovaries, fallopian tubes, and uterus) are not affected by androgen exposure and develop normally.

Classic 21-OHD has a worldwide incidence of about 1 in 5,000 to 1 in 15,000 live births (Witchell & Azziz, 2011). Two-thirds of those have a severe form known as salt-wasting or salt-losing in which there is a concurrent inability to produce aldosterone. High sodium excretion leads to profound hyponatremia, dehydration, and hyperkalemia. Glucocorticoid deficiency impairs carbohydrate metabolism, resulting in hypoglycemia and leading to hypotension, shock, and cardiovascular collapse from adrenal insufficiency. The remaining one-third has a simple virilizing form. These infants have an incomplete enzymatic block, with enough aldosterone biosynthesis to maintain fluid and electrolyte homeostasis.

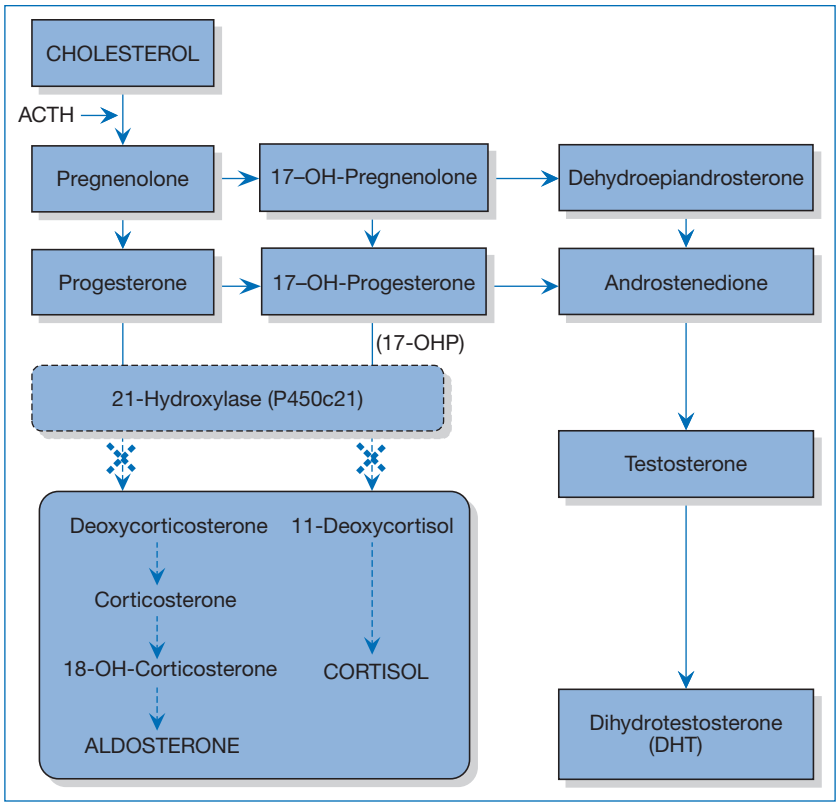

FIGURE 10.3 Pathophysiology of congenital adrenal hyperplasia caused by 21-hydroxylase (21-OHD) deficiency. A deficiency of the enzyme 21-OHD prevents the normal conversion of cholesterol to aldosterone and cortisol. Precursor steroids including 17-hydroxyprogesterone (17-OHP) proximal to the blocked step are shunted into the androgen synthesis pathway, resulting in an excess production of androgens.

ACTH, adrenocorticotropic hormone.

Clinical Manifestations. Affected female infants are usually recognized at birth by their nontypical genitals, a cardinal feature of CAH. A range of findings is possible, including clitoromegaly, posterior fusion of the labia majora with rugae, and a single perineal orifice instead of separate urethral and vaginal openings (Witchel & Azziz, 2011). In the last instance, the vagina joins the urethra above the perineum, forming a single urogenital. In severe cases, clitoral hypertrophy is so marked that it resembles a penile urethra (Figure 10.4). These infants can be mistaken for boys with bilateral cryptorchidism and hypospadias. There may also be hyperpigmentation of the genital skin resulting from excessive pituitary ACTH secretion. Male infants with 21-OHD are phenotypically normal and may not be identified in the immediate neonatal period, because the onset of adrenal symptoms is delayed until 7 to 14 days of life. Undetected infants may present to the emergency room with signs and symptoms of impending adrenal collapse: vomiting, weight loss, lethargy, dehydration, hyponatremia, hyperkalemia, hypoglycemia, hypovolemia, and shock. Infants of either sex who are untreated will undergo rapid postnatal growth and sexual precocity; those with severe enzyme deficiencies can develop salt loss and die (Speiser et al., 2010).

Diagnosis. A markedly elevated 17-OHP level is diagnostic for classic 21-OHD deficiency. Random 17-OHP levels in affected infants can reach 10,000 ng/dL (normal is <100 ng/dL). However, such high 17-OHP levels may not be reached until the second or third day of life, so a specimen drawn too early could lead to false reassurance that the infant does not have CAH. Prenatal or postnatal steroids can suppress the 17-OHP level and produce a false negative result as well. Biochemical support for the diagnosis of CAH also includes elevated serum DHEA and androstenedione levels in males and females, and elevated serum testosterone in females. Molecular genetic analysis is not usually essential for the diagnosis but may be helpful to confirm the exact type of defect and to aid in genetic counseling.

Part of the evaluation of every newborn with ambiguous genitalia is a karyotype or FISH test for sex chromosome material, and this is also true when the suspected diagnosis is CAH. Imaging studies, including pelvic and abdominal ultrasound, will determine the presence or absence of a uterus, evaluate adrenal size, and more rapidly identify the gender of the infant.

The increased serum 17-OHP levels in affected infants permit screening for the disorder using blood filter specimens on routine newborn screening panels. **Quality and Safety: The major objectives of newborn screening for CAH are the presymptomatic identification of infants at risk for the development of life-threatening adrenal crises and prevention of incorrect sex assignment of affected female infants with ambiguous genitalia.** The former is particularly important for affected boys whose initial manifestation may be adrenal crisis. All 50 states now screen newborns for CAH. False positives occur in about 1% of all tests, and can also occur in preterm infants or sick infants, both of whom have higher levels of 17-OHP (Speiser et al., 2010). The higher 17-OHP concentrations of preterm infants, sick infants, and heterozygotic carriers can overlap the levels typical of babies with nonclassic CAH (Witchel & Azziz, 2011).

Management. The newborn with CAH requires urgent expert medical attention. When the diagnosis of CAH is confirmed, physiologic replacement dosing of cortisol is initiated to overcome cortisol deficiency and to suppress ACTH and androgen overproduction, without completely suppressing the HPA axis (Pass & Neto, 2011). Aldosterone replacement maintains fluid and electrolyte homeostasis. Agents of choice in the newborn are hydrocortisone, a glucocorticoid, plus fludrocortisone, a mineralocorticoid. Further clinical management is guided by daily

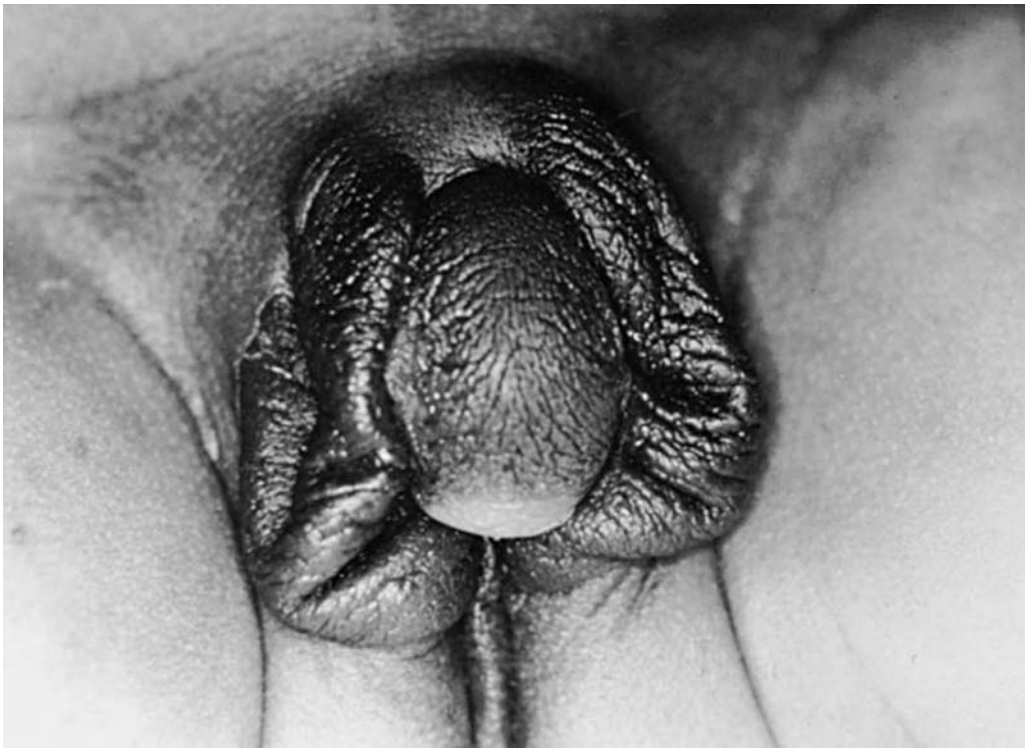

FIGURE 10.4 External genitalia of 46XX neonate with congenital adrenal hyperplasia. Note clitoromegaly with rugosed, hyperpigmented, and partly fused labioscrotal folds.

Source: Stokowski, L. (2015). Endocrine disorders. In M. T. Verklan & M. Walden (Eds.), *Core curriculum for neonatal intensive care nursing* (5th ed., pp. 632–661). Philadelphia, PA: Elsevier.

checking weight, adrenal steroid concentration, PRA, electrolytes, blood glucose, and other data. PRA should be compared against age-specific norms, because basal PRA is higher in the newborn than in older infants. Dietary sodium chloride supplementation is often necessary.

Most 46XX individuals with CAH develop a female gender identity, regardless of the degree of genital virilization present at birth, according to currently available evidence (Houk & Lee, 2012). Therefore, even in cases where babies are initially "misassigned" as boys, it is still generally recommended that these genetic females with CAH be raised as females (Brown & Warne, 2005), although some experts maintain that in extensively virilized infants, a male sex assignment should be considered (Houk & Lee, 2012). Hypertrophy of the clitoris will gradually abate with medical therapy; however, severe virilization will not be reversed. Parents of virilized female infants may have many questions about possible genital surgery. Although such surgery is not usually performed until the infant is 2 to 6 months of age, it is helpful for the parents to meet with the pediatric endocrinologist and pediatric urologic surgeon during the initial hospitalization or shortly afterward to discuss available options, one of which is to delay surgery performed for cosmetic purposes until the child is old enough to participate in the decision (Auchus et al., 2010; Intersex Society of North America [ISNA], 2006). The goals of genital surgery for virilized girls with CAH are to achieve genital appearance compatible with gender, unobstructed urinary emptying without incontinence or infections, and good adult sexual and reproductive function. After discharge, infants with CAH must be closely followed by a pediatric endocrinologist for assessments of hormone levels, blood sugar, blood pressure, growth, skeletal maturation, and other parameters necessary to guard against over- or undertreatment.

Some authorities now use the term *disorder of sex development* or *DSD related to physical changes in genitalia,* or the older term, *ambiguous genitalia,* discussed in the next section (Houk, Baskin, & Levitsky, 2019). Whether to force a specific sexual identification early is still hotly debated and often results in ethical considerations—especially the wishes of the family.

GENITALIA

Sexual Development in the Fetus

Sexual differentiation is a sequential process with three stages: (a) fertilization (determination of chromosomal sex), (b) gonadal differentiation, and (c) differentiation of phenotypic sex (internal ductal system and external genitalia; Shnorhavorian & Fechner, 2018).

At the time of conception, the sex chromosome complement of the fertilizing sperm determines the chromosomal sex.

The following events are directed by genes. During the early weeks of development, all embryos have bipotential gonads and structures for both male and female internal and external genitalia. Male-specific development requires the expression of the testis-determining gene (*SRY*) located on the short arm of the Y chromosome. This directs the gonad to differentiate to a testis, the key event in sex determination, by downstream regulation of sex-determining factors (Öçal, 2011).

Numerous other genes are required for normal gonadal development, and mutations in many of these genes (such as *SRY, WT1, SOX9, DAX-1, DMRT1,* and *SF1*) are the source of identified syndromes of gonadal dysgenesis, such as Swyer syndrome, Denys–Drash syndrome, campomelic dysplasia, dosage-sensitive sex reversal, and gonadal dysgenesis. It was formerly believed that the ovary developed as a "default" gonad (in the absence of genes for testis development), but we now know that specific genes are necessary for normal ovarian differentiation (Shnorhavorian & Fechner, 2018).

Internal Genitalia

The next events in sexual development are hormonally mediated, predicated on the established gonadal sex (Shnorhavorian & Fechner, 2018). By 7 weeks gestation, the fetus has two sets of primitive ducts that will become the internal reproductive tracts: the Müllerian (female) and Wolffian (male). In the XY fetus, the testis differentiates by the end of week 7. The embryonic testis develops two types of hormone-producing cells: the Sertoli and the Leydig cells. The Sertoli cells begin secreting Müllerian-inhibiting factor (MIF), causing the Müllerian ducts to regress. By the ninth week, testicular Leydig cells are secreting the androgens necessary for further virilization of the male fetus.

Testosterone, the major androgen produced by the testes, acts locally in high concentrations to induce development of the Wolffian ducts into the epididymis, vas deferens, and seminal vesicles. In the absence of testosterone, the Wolffian ducts regress at 11 weeks gestation. Müllerian ducts require no ovarian hormonal inducement to develop into fallopian tubes, uterus, and upper vagina. This occurs in fetuses with a normal ovary or on any side lacking a gonad.

External Genitalia

The primitive external genital structures are identical in both sexes (Figure 10.5). In this indifferent stage, a genital tubercle forms and elongates to form a phallus and urogenital sinus, surrounded by inner urogenital folds and labioscrotal swellings. Between the 8th and 14th weeks of gestation, male differentiation of the external genitalia takes place. Central to this development is availability of

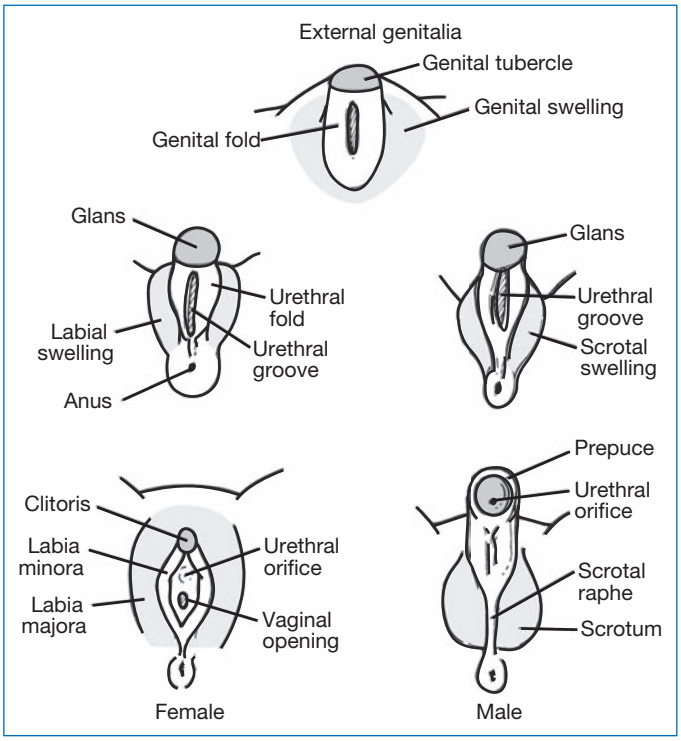

FIGURE 10.5 Development of the external genitalia.

Source: From Houk, C. P., & Lee, P. A. (2005). Intersexed states: Diagnosis and management. *Endocrinology and Metabolism Clinics of North America, 34,* 791–810. doi:10.1016/j.ecl.2005.04.014

DHT, a potent metabolite produced from testosterone by the enzyme 5 alpha-reductase-2 (5-ARD-2). With ten times the binding affinity of testosterone, DHT binds to androgen receptors in the genital tissues, stimulating fusion of the urethral folds to form the penile shaft, and the labioscrotal swellings to form the scrotum. The urogenital sinus becomes the urethra. Penile growth continues throughout gestation, and migration of the testes from the abdominal cavity to the scrotum is a late event, at 25 to 35 weeks gestation. Androgen exposure after about 14 weeks contributes to further phallic enlargement (Shnorhavorian & Fechner, 2018).

In the absence of DHT, feminization of the external genitalia occurs. The phallus becomes a clitoris, and the labioscrotal swellings remain unfused to form the labia majora and minora. The urogenital sinus develops into the lower vagina and urethra. Feminine external genital development is complete by 11 weeks of gestation. Androgen exposure after this critical period can promote growth of the clitoris but does not cause labial fusion or the development of a penile urethra (Shnorhavorian & Fechner, 2018).

GENERAL PRINCIPLES OF MANAGEMENT OF DISORDERS OF SEXUAL DEVELOPMENT

The fact that doctors and nurses are not quite sure if one's long-awaited newborn baby is a boy or a girl must surely be one of the most incomprehensible things that parents can hear in the delivery room. This situation requires a high degree of sensitivity and tact. Many infants are identified prenatally following ultrasound recognition of genital ambiguity or a karyotype/phenotype discordance, and these families will be prepared, to some degree, for the experience of having a baby of uncertain sex. Others will be taken completely by surprise. In spite of the family's desire for a quick answer, no attempt should be made by medical professionals at the time of birth to guess the sex of the baby (Ogilvy-Stuart & Brain, 2004). The extreme phenotypic heterogeneity seen in DSDs makes it impossible to accurately predict either the diagnosis or the karyotype from a brief genital examination (Houk & Lee, 2005). Neonates who do not have health concerns requiring intensive care monitoring or treatment should not be transferred to the NICU. Admission to the NICU heightens the parents' anxiety unnecessarily and impairs parent–infant bonding (ISNA, 2006).

The Lawson Wilkins Pediatric Society and the European Society for Paediatric Endocrinology recently established an International Consensus Conference on Intersex. The result was a consensus statement on management of DSDs (Lee, Houk, Ahmed, & Hughes, 2006). That document represents the first agreed-on set of guiding principles for approaching and managing the newborn with a DSD.

Clinical Manifestations. Essential to the evaluation of the neonate with genital ambiguity is obtaining a detailed family history. Any of the following might suggest a congenital or inherited DSD: maternal virilization or ingestion of hormones or oral contraceptives during pregnancy; consanguinity; history of urologic abnormalities, infertility, or genital ambiguity in other family members; or previous neonatal deaths that might suggest an undiagnosed adrenal crisis. Dysmorphic features suggest the possibility of a syndrome.

A detailed assessment of the genitalia should be conducted. This and all subsequent examinations should respect the privacy of the infant and the family as much as possible, avoiding overexposure of the infant even for educational purposes (Auchus et al., 2010). Because of considerable overlap in the genital anatomy among DSDs, the physical assessment alone does not permit a firm diagnosis (Shnorhavorian & Fechner, 2018). However, some assessment findings can provide clues to the underlying pathophysiology and guide the diagnostic process in one direction or another. A precise description of the anatomy is more useful than simply staging classifications. If preferred, however, the degree of virilization can be documented by Prader staging from a phenotypic female with mild clitoromegaly (Prader stage II) to phenotypic male with glandular hypospadias (Prader stage V; Figure 10.6). Look for symmetry or asymmetry of the genitalia, which provides an important clue. The presence of a uterus can be determined by digital rectal examination as an anterior midline cordlike structure.

Gonads. Determine whether gonads are palpable. The presence or absence of palpable gonads helps to differentiate the major categories of DSDs. An apparent male infant with bilateral or a single impalpable testis with hypospadias should be considered as having a potential DSD until proven otherwise. A palpable gonad excludes the diagnosis of virilized genetic female (46XX) with CAH. A gonad palpated below the external inguinal ring is presumed to contain testicular tissue. Because ovaries are rarely palpable, a unilateral gonad is usually a testis or occasionally an ovotestis. To palpate testes, place fingers flat from the internal ring and milk down into the labioscrotal folds. Gonads may be situated high in the inguinal canal, requiring a careful examination. Sweep the fingers down along the line of the inguinal canal on each side, beginning well above the site of the internal inguinal ring. A gonad milked down by this maneuver is gently grasped by the other hand and its size and consistency are noted. Ovotestes are softer and

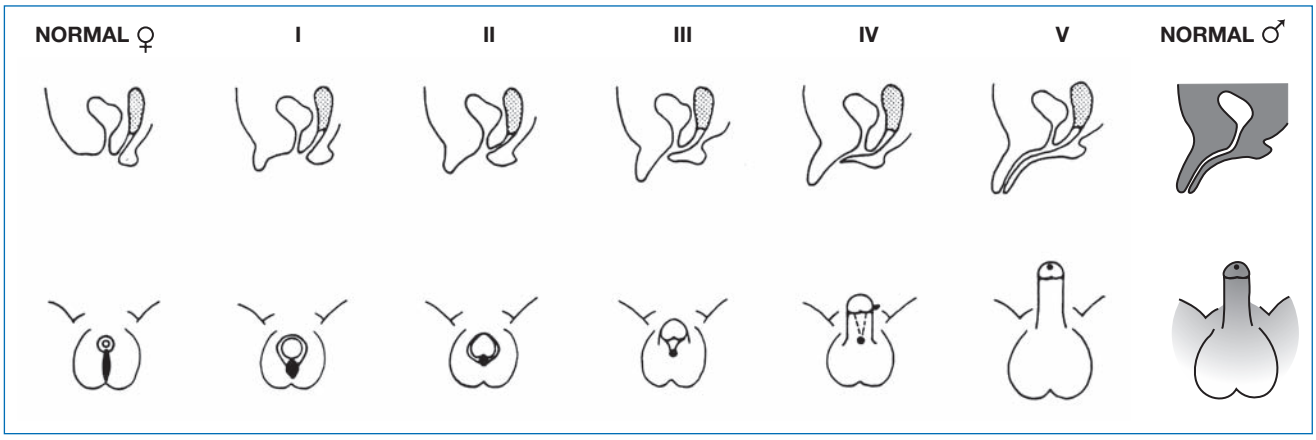

FIGURE 10.6 Degrees of genital virilization according to the stages of Prader. The upper panel shows sagittal view and the lower panel shows perineal view.

less homogeneous than testes (Brown & Warne, 2005). Bilateral absence of the testes is known as cryptorchidism.

Phallus. Phallic size should be measured with a straight-edge ruler, depressing the fat pad and measuring the stretched length from pubic tubercle to tip of penis, not including the foreskin. Both length and mid-shaft diameter of the penis should be noted. Chordee, ventral curvature of the penis caused by residual urethral tissue that tethers the phallus to the perineum, should be noted because it can reduce the apparent length of the penis (Shnorhavorian & Fechner, 2018). The actual position of the urethral meatus and the severity of hypospadias, if present, should be determined.

Clitoral size should also be measured when clitoromegaly is present. Clitoral length greater than 9 mm in term infants is considered excessive. Clitoral size often appears large in preterm infants because breadth remains constant from 27 weeks onward. A prominent, but not truly enlarged, clitoris, or a normally sized penis concealed by an abundance of prepubic fat are two normal assessment findings that sometimes prompt referrals for genital ambiguity (Houk & Lee, 2005).

Labioscrotal Folds. Labial fullness, a benign finding, is another feature occasionally mistaken for genital ambiguity. The labioscrotal folds are examined for fusion, which starts posteriorly and moves anteriorly, increasing the anogenital distance. The perineum is inspected by gently separating the labia and using an exam light to confirm the presence of separate urethral and vaginal openings or a single urogenital orifice (an opening connected to both urinary and genital systems). Visualization of voiding is helpful. If skin tags with slightly bluish hue are seen, a hymen and vagina are present. Note rugosity or hyperpigmentation of the labioscrotal fold, signifying hypersecretion of ACTH associated with CAH. Other variations include a bifid scrotum (a deep midline cleft) or a shawl scrotum (scrotum surrounds the penis like a shawl).

Diagnostic Studies. DSDs are diagnosed with a combination of biochemical, hormonal, imaging, and molecular testing. Many diagnostic algorithms have been published, but no single algorithm is perfect for all circumstances (Lee et al., 2006). The principal aim of an initial investigation is to rule out a life-threatening illness such as CAH, which can precipitate an adrenal crisis. Such testing includes serum 17-OHP level (after 24–48 hours of age), electrolytes, glucose, baseline levels of testosterone, DHT, and other steroid precursors (progesterone, DHEA, delta 4-androstenedione, and 17 alpha-hydroxypregnenolone). A karyotype with X- and Y-specific probe detection is obtained from all infants, even if a prenatal karyotype is available (Allen, 2009).

A urinary steroid profile is helpful in the diagnosis of disorders of steroid biosynthesis. Other investigations that may be warranted include ACTH stimulation test, PRA, and serum MIF, LH, and FSH. An hCG stimulation test is undertaken to delineate a block in testosterone biosynthesis from androstenedione (17 beta-hydroxysteroid dehydrogenase deficiency) or conversion of testosterone to DHT (5 alpha-reductase deficiency). An hCG test involves measuring baseline levels of testosterone and its precursors DHEA or DHEA sulfate and androstenedione and its metabolite DHT. One to three intramuscular injections of high-dose hCG are given at 24-hour intervals, and repeat testosterone levels are drawn at 72 or 24 hours after the last injection (Ogilvy-Stuart & Brain, 2004).

Imaging studies include abdominopelvic ultrasound (to determine the presence or absence of a uterus, to visualize the presence or absence of gonads in the inguinal region, and to assess the Müllerian anatomy), genitourethrogram (to delineate the anatomy of the vagina and urethra, and where the vagina opens into the urogenital sinus), and pelvic MRI. Laparoscopic exploration with gonadal biopsy may be necessary to evaluate gonadal histology. Finally, molecular analysis may be required to arrive at a definitive diagnosis for some disorders, although molecular diagnosis continues to be limited by cost, accessibility, and quality control (Lee et al., 2006).

Interpretation of Findings. The most common cause of genital ambiguity in the newborn is 21-OHD deficiency. This form of CAH, responsible for over 90% of cases of ambiguous genitalia, presents with a virilized XX (female) infant and should be suspected in the presence of a virilized infant with a uterus and no palpable gonads (Öçal, 2011).

Among the remainder of cases of ambiguous genitalia, the most common diagnoses are gonadal dysgenesis, followed by partial androgen insensitivity syndrome (PAIS) and testosterone biosynthetic disorders. Symmetrical external genitalia, with or without palpable gonads, and no uterus, suggests an undervirilized male (Öçal, 2011). A micropenis should prompt investigation for hypopituitarism or growth hormone deficiency, particularly in the presence of hypoglycemia (Shnorhavorian & Fechner, 2018).

It is not always possible to reach a diagnosis in the undervirilized male infant. In a study of 67 XY infants with external sexual ambiguity, testicular tissue, and/or an XY karyotype, in 52% of cases, no diagnosis could be reached, despite an exhaustive clinical and laboratory workup, including sequencing of the androgen receptor (Morel et al., 2002). Provisional diagnostic groupings can be determined based on the presence or absence of a uterus, symmetry of the external genitalia, and presence of gonads (Table 10.1), providing a basis for more focused additional investigations (Brown & Warne, 2005).

Talking With Families. Optimal care of the infant with a DSD involves a well-coordinated team approach. The team comprises at minimum the attending neonatologist, neonatal nurse, endocrinologist, pediatric surgeon/pediatric urologic surgeon, social worker, counselor or other mental health professional, and, in some instances, geneticist. The initial contact with parents of

TABLE 10.1

DIAGNOSTIC GROUPING SUGGESTED BY ASSESSMENT FINDINGS

Diagnostic Grouping	Assessment Finding		
	Uterus	Gonads	External Genitalia
CAH (21-OHD) virilized female	Present	Not palpable	Symmetrical hyperpigmented
Undervirilized male (PAIS or testosterone biosynthetic defect)	Absent	Palpable	Symmetrical
Gonadal dysgenesis (with Y chromosome) ovotesticular DSD	Present	Palpable	Asymmetrical

21-OHD, 21-hydroxylase; CAH, congenital adrenal hyperplasia; DSD, disorder of sex development; PAIS, partial androgen insensitivity syndrome.

a newborn with a DSD is extremely important. This interaction should emphasize that a DSD is not a shameful condition and does not preclude the child from becoming a well-adjusted, functional adult, who can be expected to lead a fulfilling life (Houk & Lee, 2012). A single person should be identified to communicate diagnostic findings and plans with the family. When discussing possible diagnoses with the family, language must be carefully chosen. The terms *hermaphrodite* and *pseudohermaphrodite* are outdated, confusing, and perceived as distasteful by many (Lee et al., 2006). These words should not be used, and instead, accurate, informative terms that describe the infant's diagnosis should be used. A clear explanation of sexual development in the fetus will help parents understand how an infant can be born with atypical genitalia, an important component of parental coping (Houk & Lee, 2005). It is helpful to explain that the appearance of the external genitalia is determined by prenatal androgen exposure, and not the molecular sex (Witchel & Azziz, 2011).

It is the parents who have the responsibility to make or defer decisions about care for their infant with a DSD, including gender-of-rearing (Houk & Lee, 2005). The role of the healthcare team is to provide information, to share and explain all diagnostic findings, to inform parents of all available options, and to support the parents in the decision-making process. The approach should be family-centered as well as culturally sensitive (Thyen, Richter-Appelt, Wiesemann, Holterhus, & Hiort, 2005). Family concerns must be respected and addressed in strict confidence (Auchus et al., 2010). A relationship of trust is paramount, and this requires open and honest communication and full disclosure of available information (Shnorhavorian & Fechner, 2018), including candid discussion of the controversies and dilemmas concerning gender assignment and early genital surgery. Parental acceptance of the child with a DSD and condition are key determinants of a favorable outcome (Houk & Lee, 2012). Healthcare professionals must also recognize and respect the cultural and psychosocial influences on parents' decisions about care for their infant (Shnorhavorian & Fechner, 2018).

Gender Assignment. Parents are naturally anxious to find out their baby's gender so that they can name the baby and announce the birth to family and friends. Nevertheless, it must be sensitively communicated that although their distress is acknowledged, when gender is in doubt, a gender-of-rearing decision is one with lifelong implications and cannot be made in haste. Gender assignment must be deferred until expert evaluation of the newborn takes place and sufficient data are available for a fully informed decision (Lee et al., 2006; Shnorhavorian & Fechner, 2018).

Unfortunately, some tests required for evaluation of a DSD must be sent out to referral laboratories, and the long wait for results can be frustrating for the parents. It is helpful if an experienced mental health professional can meet very early with the parents to help them formulate what to tell family and friends in the interim (Ogilvy-Stuart & Brain, 2004). All infants should receive a gender assignment as soon as the best course is reasonably determined (Lee et al., 2006). Questions about the infant's future management and treatment needs, gender identity/gender role development, and potential long-term outcomes should be addressed by clinicians who have extensive experience with DSDs.

DISORDERS OF SEXUAL DEVELOPMENT

A DSD is a misalignment, and therefore leads to incongruence between molecular, gonadal, and phenotypic sex (Houk & Lee, 2012). Most DSDs result from one of two events: either a failure in one of the steps of the male sexual developmental pathway, or the exposure of an XX fetus to androgens during a sensitive period of development. Less frequent are DSDs resulting from gonadal differentiation, chromosomal disorders, and syndromes associated with ambiguous genitalia (Shnorhavorian & Fechner, 2018). The genes and multigenic factors responsible for DSDs are just beginning to be understood, but this information has yet to prove beneficial in terms of clinical management.

46XX DSD Trimester

The most frequently encountered DSD in the neonate is the virilized female, or the 46XX infant with ambiguous external genitalia but normal female internal structures. The most common etiology is CAH, caused by 21-OHD deficiency. This enzyme deficiency results in an overproduction of androgens at a critical stage of development, causing masculinization of the external, but not the internal (ovaries, uterus, fallopian tubes), genitalia. In the most severe cases, the excess androgens also prevent the vagina from fully descending into the perineum, leaving a common urogenital canal (see section, Adrenal Disorders in the Neonate).

Other possible, yet rare, causes of virilization of external genitalia in the 46XX infant are placental aromatase deficiency, maternal androgen-producing or adrenal tumors, and maternal medications with androgenic action taken during pregnancy.

46XY DSD

The combination of a 46XY karyotype with ambiguous genitalia results from a failure in one of the steps involved in the synthesis or response to testosterone during sexual differentiation and penile growth. These infants have bilateral testicular development, but incomplete virilization of the internal or external genitalia. This results in an external phenotype ranging from completely female to isolated hypospadias or cryptorchidism. Another condition associated with incomplete virilization in the XY male is cloacal exstrophy, a defect of embryogenesis involving exstrophy of the bladder. Although not a DSD, significant ambiguity of external genitalia may be present. In most cases of 46 XY DSD, it has not been possible to determine the causative genetic mutation (Houk & Lee, 2012).

Androgen Insensitivity Syndrome

Pathophysiology. Androgen insensitivity syndrome (AIS) is caused by a loss-of-function mutation in the androgen receptor gene located on the long arm of the X chromosome. More than 300 different mutations have been identified (Shnorhavorian & Fechner, 2018). Both testosterone and its target tissue metabolite, DHT, must bind to androgen receptors to masculinize the genital tissues. When androgen receptor activity is impaired, androgen binding is insufficient. One variant of AIS is receptor negative: Cytosol receptors are incapable of binding DHT. Another variant is receptor positive: Receptors are able to bind DHT, but this does not result in normal differentiation. Both internal Wolffian structures and external genitalia fail to respond to high levels of testosterone and DHT. There are partial and complete forms of the disorder, resulting in different degrees of undervirilization. In PAIS, the clinical phenotype varies considerably and often parallels the severity of androgen resistance, but genotype-phenotype correlations have not been found.

Clinical Manifestations. Infants with PAIS have undervirilization ranging from simple hypospadias to microphallus with a labia majora–like bifid scrotum, undescended testes, and a urogenital sinus. No visible features distinguish PAIS from other causes of incomplete masculinization. Infants with complete androgen insensitivity (CAIS) are born with apparently female genitalia.

However, these neonates may have palpable inguinal or labial masses, which further testing will reveal to be testes. Some may also have a short, blind-ending vagina.

Diagnosis. The diagnosis of CAIS is missed in the newborn period unless the infant presents with bilateral masses in the labia or inguinal canals or a boy was expected based on a prenatal karyotype. CAIS might also be discovered at the time of inguinal hernia repair, or there may be a history of similarly affected family members. Important investigations include a karyotype, levels of testosterone, DHT, and LH. In PAIS, the ratio of androstenedione to testosterone is normal. Testosterone, estradiol, and LH are normal or high: FSH is usually normal.

Androgen receptor (AR) binding assays are not always helpful, because normal ligand binding does not rule out androgen insensitivity caused by mutations in other domains of the androgen receptor (Shnorhavorian & Fechner, 2018). Less than half of the infants with suspected PAIS have abnormal androgen binding; those with normal binding may have a defect in DNA binding or transcriptional activation (Misra & Lee, 2005). A test for direct sequencing of the AR for mutational analysis is commercially available, but AR mutations are not always found in PAIS (Shnorhavorian & Fechner, 2018). Imaging studies reveal the absence of female internal reproductive structures (uterus, fallopian tubes). Two normal testes are present.

Management. Infants with CAIS have unambiguously female external anatomy and are raised in the female gender. Testes are removed (usually after puberty) to prevent later malignancy. The gender assignment of infants with PAIS can be more complex and is often based on the severity of the phenotype (Misra & Lee, 2005). When the phenotype is predominantly male, a male sex rearing is recommended. However, no consensus exists for the management of infants with severe perineoscrotal hypospadias and microphallus. The detection of somatic mutations in AIS is of importance for correct sex assignment because the presence of a functional wild-type AR receptor can induce virilization at puberty (Köhler et al., 2005). When it is contemplated to rear as male sex, a therapeutic trial with pharmacologic doses of androgen, especially in those with an identified AR mutation, is often used to predict potential androgen responsiveness at puberty. If the phallus does not grow in response to testosterone, some experts would recommend consideration of a female gender assignment. However, many experts now believe that, given the putative influence of prenatal androgen exposure on the developing CNS, and the possibility that the child will develop a male gender identity, it is more prudent to raise these infants as boys.

Testosterone Biosynthetic Defects

Pathophysiology. Defects in the chain of steroidogenic enzymes involved in the testosterone biosynthesis pathway result in insufficient androgen concentrations during fetal development. Disorders include congenital lipoid adrenal hyperplasia (CLAH), 3 beta-HDD, 17 alpha-hydroxylase/17,20 lyase deficiency, and 17 beta-hydroxysteroid dehydrogenase deficiency (17 beta-HSD). CLAH is caused by a defect in the steroidogenic acute regulatory (StAR) protein, responsible for transporting cholesterol to the inner membrane of the mitochondria. Insufficient testosterone in affected males leads to underdeveloped Wolffian duct structures and external male anatomy. Müllerian structures are absent because there is normal testicular MIF production.

Clinical Manifestations. Male infants with CLAH present with complete adrenal insufficiency: vomiting, weight loss, and hypotension. Genital appearance is primarily female. Infants with 3 beta-HDD can present with varying degrees of genital ambiguity and evidence of salt-losing crisis (see 21-OHD). Infants with 17 alpha-hydroxylase/17,20 lyase deficiency have genital ambiguity, whereas patients with primary 17 alpha-hydroxylase deficiency also have hypertension. Male infants with 17 beta-HSD present with what appear to be external female genitalia that may include mild clitoral enlargement. An inguinal hernia may be present, possibly the only finding that will bring the infant to medical attention.

Diagnosis. General laboratory investigations in suspected testosterone biosynthetic defects include chromosomes, baseline levels of testosterone, androgen precursors and DHT, and levels of steroids and steroid precursors. An hCG stimulation test can be performed to measure the ratio of androstenedione to testosterone; an elevated ratio suggests 17 beta-HSD deficiency. In CLAH, ultrasound, CT, or MRI may show enlarged, lipid-laden adrenal glands (Shnorhavorian & Fechner, 2018).

Management. Acute management of these disorders requires full steroid replacement with both glucocorticoids and mineralocorticoids. In CLAH and 3 beta-HDD, general supportive measures may be necessary, as severe adrenal insufficiency can cause rapid metabolic decompensation if the disorder is not recognized at birth (Misra & Lee, 2005). Genetic XY infants with CLAH are raised in the female gender. Children with 17 beta-HSD often virilize significantly at puberty owing to increased peripheral conversion of androstenedione to testosterone by 17 beta-HSD isoenzymes, making gender assignment of those diagnosed as neonates a less straightforward decision.

5-Alpha-Reductase-2 Deficiency

Pathophysiology. 5-ARD-2 deficiency is an autosomal recessive disorder caused by more than 20 different mutations of the *5-ARD* gene. 5-ARD-2 is an enzyme found in the genital skin and fibroblasts of the developing fetus, without which testosterone is not converted to DHT, and fetal external genitalia do not virilize. Development of the internal structures is unaffected because DHT is not required, so the Wolffian ducts differentiate normally in response to testosterone and the Müllerian ducts regress. At puberty, the external genitalia become virilized and fertility is possible (Misra & Lee, 2005).

Clinical Manifestations. The spectrum of findings ranges from mild (isolated micropenis or hypospadias) to severe (a female phenotype with clitoromegaly, mild rugation, or pigmentation) undervirilization (Figure 10.7). Testes are intact and are found in the inguinal canals or labioscrotal folds, or are retained in the abdomen. The uterus and fallopian tubes regress because of normal secretion of MIS. Wolffian duct differentiation is not affected because DHT is not required. Male internal ducts terminate either in a blind pseudovaginal pouch or on the perineum.

Diagnosis. Diagnosis is made by assessing the ratio of testosterone to DHT following an hCG stimulation test. A normal T/DHT ratio is less than 4 to 1. In 5-ARD-2 deficiency, this ratio is elevated to higher than 14 to 1 (Shnorhavorian & Fechner, 2018). The hCG stimulation test also rules out other causes of undervirilization, such as Leydig cell hypoplasia and testosterone biosynthetic defects. Analysis of 5-ARD-2 activity in genital skin fibroblasts provides a definitive diagnosis.

Management. Boys with 5-ARD-2 respond to endogenous testosterone and undergo virilization and penile growth at puberty. The mechanism behind this late virilization may be extraglandular DHT formation due to peripheral conversion of increased testicular testosterone by unaffected isoenzymes. For this reason, it is recommended that when the diagnosis is made in the newborn period, a male sex assignment is usually made.

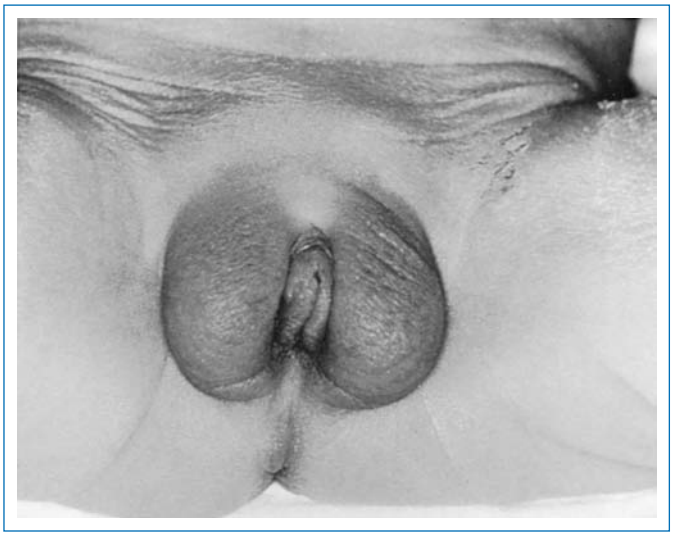

FIGURE 10.7 External genitalia of 46XY neonate with 5 alpha-reductase deficiency. Undervirilization is so severe in this infant that the phenotype is almost completely female, with labia majora–like bifid scrotum and severe microphallus.

Source: From Stokowski, L. (2015). Endocrine disorders. In M. T. Verklan & M. Walden (Eds.), *Core curriculum for neonatal intensive care nursing* (5th ed., pp. 632–661). Philadelphia, PA: Elsevier.

Gonadal Dysgenesis

This group of disorders is usually associated with chromosomal anomalies or mutations or deletions of genes responsible for sexual differentiation. Karyotypes producing gonadal dysgenesis include 46XY, 46XX, 46XY/46X, and mosaic forms including the Y chromosome. Gonadal dysgenesis can occur as an isolated condition or as part of a complex syndrome such as Fraser, Denys–Drash, or campomelic dysplasia (Brown & Warne, 2005).

Pathophysiology. Dysgenetic gonads are characterized by variable degrees of immaturity or dysfunction, which can manifest in a wide range of genital ambiguity. Gonadal dysgenesis is considered partial or incomplete when the testes are dysgenic or incompletely formed, and complete when the gonads are streaks containing only stromal tissue. Mixed gonadal dysgenesis occurs when one gonad is a streak and the other is a well-formed testis. The internal ducts correlate with the ipsilateral gonad. On the side of a streak gonad, a fallopian tube and a hemiuterus will develop, and on the side of a normal testis, the vas deferens and epididymis will form.

Clinical Manifestations. The external genitalia are highly variable depending on how much testosterone is produced. In mixed gonadal dysgenesis, the external genitalia are asymmetric, appearing male on one side and female on the other. A vagina and uterine cavity may be present. Complete (or pure) gonadal dysgenesis is a form of sex reversal that results in unambiguously female genitalia with features of Turner's syndrome. These infants might not be identified in the newborn period unless a discrepancy is noted between a prenatal karyotype (46XY) and appearance of the genitals.

Diagnosis. Determining the sex chromosome complement by FISH testing is the most important diagnostic test. Imaging studies, genitography, or laparoscopy is used to define the internal anatomy. Gonadal histologic analysis is necessary to differentiate gonadal dysgenesis from ovotesticular DSD, a condition wherein elements of both testes and ovaries are present in the same individual (see Ovotesticular DSD).

Management. Determining the sex of rearing for the infant with partial or mixed gonadal dysgenesis can be a difficult decision, one that is typically based on the degree of virilization and details of the internal anatomy. When a uterus is present, the female sex assignment may be preferred. Most infants with complete gonadal dysgenesis are raised as females.

Ovotesticular DSD

In ovotesticular DSDs, both ovarian and testicular components are present in the same individual. Possible combinations include an ovary on one side and a testis on the other, an ovary or testis with an ovotestis, or two ovotestes. More than half the affected babies will have an XX karyotype. This condition was formerly known as true hermaphroditism, a label that is considered outdated.

Pathophysiology. The amount of testosterone produced by the testicular tissue that is present determines the degree of differentiation of Wolffian ducts, regression of Müllerian ducts, and virilization of external genitalia. The internal ducts usually parallel the ipsilateral gonadal histology. Ovarian tissue can be normal.

Clinical Manifestations. Asymmetry of the external genitalia is a hallmark of ovotesticular DSD. Genital ambiguity ranges from a female phenotype with slight clitoromegaly to a mildly undervirilized male phenotype. The most common presentation is marked genital ambiguity: microphallus with penoscrotal or perineoscrotal hypospadias, fusion of labioscrotal folds, and cryptorchidism (Misra & Lee, 2005).

Diagnosis. FISH testing is used to determine the sex chromosome complement. Imaging studies are used to define the internal anatomy. To diagnose ovotesticular dysgenesis, the presence of functional ovarian tissue containing follicles and testicular tissue with distinct seminiferous tubules must be established (Misra & Lee, 2005). Laparoscopy with gonadal biopsy is necessary at some point to confirm the diagnosis.

Management. Principles of management for infants with true ovotesticular DSD are similar to those of gonadal dysgenesis.

PANCREAS

The pancreas is both an exocrine and endocrine gland. The endocrine pancreas is responsible for hormonal regulation of blood glucose levels. The endocrine functions are performed by clusters of cells called islets of Langerhans that include alpha, beta, and delta cells. Hormones secreted by the endocrine pancreas include glucagon, insulin, amylin, and somatostatin.

Fetal insulin, present by 8 to 10 weeks gestation, is secreted in response to both glucose and amino acids. The fetus is critically dependent for growth on its own supply of insulin, which does not cross the placenta. Insulin stimulates uptake of glucose by muscle and adipose tissue. The fetal pancreas becomes progressively more responsive to glucose late in gestation and beta-cell mass increases markedly. At birth, when maternal glucose supply ceases, the neonate's blood glucose level declines, along with plasma insulin. A concomitant surge in the counter-regulatory hormones epinephrine and glucagon sets in motion the production of glucose that will sustain the neonate until milk feeding is established.

The exocrine portion of the pancreas constitutes 80% of the total gland. Acinar cells secrete digestive enzymes including trypsin, lipase, and amylase into the duodenum. Epithelial cells along the pancreatic ducts secrete bicarbonate and water that neutralize gastric acid.

DISORDERS OF PANCREAS

Rare pancreatic disorders in the newborn include congenital anomalies such as pancreatic agenesis, pancreatic hypoplasia, and annular pancreas. Disorders of the endocrine pancreas include neonatal diabetes mellitus (NDM) and hyperinsulinism, as well as the developmental disorder of the pancreas seen in the infant of the diabetic mother (IDM). The most common newborn disorder of the exocrine pancreas is cystic fibrosis (CF).

Infant of a Diabetic Mother

Diabetes in pregnancy is on the rise, paralleling the marked increase in people with type 2 diabetes and prediabetes (Homko, 2010). More newborns will be at risk for the problems associated with glucose intolerance and abnormal glucose regulation during pregnancy if this epidemic does not abate.

Pathophysiology. If maternal glycemic control is poor in the third trimester, high circulating maternal glucose levels chronically stimulate the fetal pancreas to release insulin, leading to fetal fat deposition. Maternal glucose homeostasis is a key determinant of fetal size (Walsh, Mahony, Byrne, Foley, & McAuliffe, 2011). Fetal macrosomia is more likely to occur in women whose hyperglycemia occurs episodically, particularly after a meal, and from the transfer of lipids from mother to fetus (Hay, 2012). At birth, the neonatal beta-cells take time to adjust to the lower circulating glucose level, and continue to secrete insulin, preventing the mobilization of glycogen and fat as sources of glucose. This failure of normal metabolic adaptation places the baby at risk of hypoglycemia. Hyperinsulinemia, regardless of whether the mother had type 1 or type 2 diabetes, can result in increased glucose utilization, decreased glucose production, and reduced availability of alternate substrates in the newborn (Hay, 2012).

Excess fetal insulin may also be the cause of delayed maturation of type II alveolar cells and pulmonary surfactant deficiency seen in some IDMs. Transient functional anomalies of the heart, including cardiomyopathy and intraventricular septal hypertrophy, begin in utero with glycogen loading of the septum. A delayed adaptation in parathyroid regulation after birth is the source of hypocalcemia and hypomagnesemia of the IDM. An increase in fetal erythropoiesis leading to polycythemia in the IDM is common, but its etiology is unknown. Hyperbilirubinemia results from the presence of excess hemoglobin, in turn, resulting in a larger than normal bilirubin load.

The higher rate of congenital anomalies associated with diabetic pregnancy is related to maternal glycemic control at the time of conception and during early gestation, when organogenesis is taking place. Congenital malformations associated with maternal diabetes include those of the CNS (anencephaly, meningomyelocele, encephalocele, caudal dysplasia), the heart (transposition of the great vessels, coarctation of the aorta, ventricular septal defects, atrial septal defects), the kidneys (hydronephrosis, renal agenesis), and the gastrointestinal tract (duodenal atresia, small left colon syndrome).

Clinical Manifestations. As a result of fat accumulation in late gestation, affected fetuses can develop macrosomia, with birth weights that are not in proportion with their length and head circumference measurements. Intrauterine growth restriction is a less common presentation, seen in advanced maternal diabetic vascular disease. Skin tones may be ruddy with sluggish capillary refill. The neonate may present in respiratory distress. If there is a history of difficult vaginal delivery with shoulder dystocia, the infant may present with musculoskeletal or peripheral nerve findings, suggesting fractured clavicle or humerus or brachial plexus palsy. With the latter condition, the affected arm is held limply at the side, and movements, including Moro responses, are asymmetric. Deep tendon reflexes are absent. Crepitus may be palpated along the clavicle if a fracture is present.

Diagnosis. Macrosomia at birth is a good marker for detecting the infant at risk for neonatal morbidities related to maternal diabetes. In spite of the IDM's size, it is also important to determine gestational age to assess the risk of problems related to prematurity. **Quality and Safety: The IDM must be monitored for hypoglycemia, which usually occurs within an hour or two of birth. Objective measurements of blood and plasma glucose should be used rather than relying on symptoms of hypoglycemia, because the latter are nonspecific and unreliable.** Point-of-care blood glucose test results indicating hypoglycemia (<40 mg/dL in the newborn) should be verified with a serum laboratory glucose; however, treatment should not be delayed while awaiting the results of the laboratory test. If no treatment is initiated and the serum glucose confirms hypoglycemia, valuable time is wasted, but if treatment is begun and the serum glucose is actually higher than the point-of-care glucose, the treatment is relatively benign.

Additional testing required for the IDM is a serum calcium concentration and, if this is low, a serum magnesium is done. Hemoglobin level should be measured with a venous, rather than a capillary, blood sample. Additional diagnostic tests will depend on findings of the initial physical examination.

Management. Close consultation between maternal and infant caregivers, particularly at the time of labor and delivery, is a necessary ingredient for successful management of the IDM (Hawdon, 2011). Unless life-threatening complications, such as perinatal asphyxia, are present, prevention of hypoglycemia is typically the primary concern in the early management of the IDM. Early, frequent milk feedings in stable infants are ideal, if tolerated. Infants born preterm may display immature feeding skills, despite their large size, and require gavage feedings. **Quality and Safety: Severe or persistent hypoglycemia is managed with intravenous glucose boluses, followed by continuous glucose infusion starting at 6 to 8 mg/kg/minute.** Glucose infusions must be weaned slowly, with close monitoring of blood glucose levels, as the neonate acquires the ability to sustain a normal blood sugar level between feedings.

Neonatal Diabetes Mellitus

NDM is a rare disorder manifested by persistent, insulin-sensitive hyperglycemia occurring as early as the first week of life and lasting more than 2 weeks. About half of all cases of NDM are of the transient form (TNDM), and half the permanent form (PNDM). Recent data suggest that the frequency of NDM is 1 in 100,000 live births (Grulich-Henn et al., 2010).

Pathophysiology. The fundamental problem in NDM is a failure of the pancreas to release sufficient insulin in response to high blood glucose levels. NDM is unrelated to the presence of anti-insulin or anti-islet cell antibodies. In TNDM, diabetes develops within days of birth and resolves again within weeks or months before recurring, in a milder form, in late childhood. PNDM develops within days to months after birth and persists throughout life. Most cases of PNDM are caused by transcription factors involved in beta-cell development and in insulin secretion, the glucose-sensing enzyme glucokinase, and a gene-regulating immune response. About half of the affected neonates have activating mutations of the KATP channel—KCNJ11 and ABCC8

(Edghill, Flanagan, & Ellard, 2010). Most cases of TNDM are caused by one of three genetic mechanisms: a paternal uniparental isodisomy of chromosome 6, a paternally inherited duplication of 6q24, or a maternal methylation defect within the same region (Sperling, 2006).

Clinical Manifestations. A common feature of NDM is intrauterine growth restriction, a result of insufficient insulin secretion and subsequent failure to thrive in utero. Intrauterine growth restriction in infants with deficient insulin secretion in utero highlights the importance of insulin as a growth hormone. In addition to being small for gestational age, infants with NDM exhibit hyperglycemia, glycosuria, osmotic polyuria, dehydration, and minimal ketoacidosis.

Diagnosis. The diagnosis is made by demonstrating hyperglycemia with low levels of insulin, insulin-like growth factor-1, and C-peptide. The hyperglycemia responds to insulin infusion. Antibodies to insulin or islet cells are absent. If there are signs and symptoms of malabsorption, pancreatic agenesis should be ruled out by abdominal ultrasound. TNDM and PNDM cannot be differentiated, based on clinical course, in the neonatal period; genetic testing for chromosome 6 anomalies is required. A genetic diagnosis is worth the expense in infants with NDM (Greeley et al., 2011). If the neonate is shown to have a mutation of the KATP channel, treatment with oral sulfonylureas, rather than insulin, is possible, which is tremendously beneficial to the child's glucose control and quality of life.

Management. Insulin therapy is necessary in some affected infants to manage hyperglycemia and achieve adequate growth, initially by continuous drip and transitioning to subcutaneous injection of an intermediate-acting insulin preparation when condition permits. A high caloric intake can be difficult to maintain. In some infants, insulin therapy can be withdrawn after a period of time when it is observed that exogenous insulin induces hypoglycemia. The course of disease in NDM is highly variable. Some infants with TNDM will have spontaneous recovery with no further disease recurrence, whereas others will have apparent remission with recurrence of permanent disease in late childhood. Infants with PNDM have no remission of their disease.

The opportunity for parents to speak with the pediatric endocrinologist and geneticist should be provided, if possible, for information and guidance about both the cause of NDM and the plans for continuing care for their infant. Close follow-up is essential even if the diabetes has resolved because of the high rate of recurrence later in childhood.

Congenital Hyperinsulinism

Congenital hyperinsulinism is not a single disorder, but a group of disorders with the common feature of hyperinsulinemic hypoglycemia, secondary to inappropriate secretion of insulin (Arnoux et al., 2011). It is the most frequent cause of severe, persistent hypoglycemia in the newborn, with an incidence of 1 in 30,000 to 50,000 live births (Werny, Taplin, Bennett, & Pihoker, 2018). Several different genetic forms have been described. Between 10% and 15% of congenital hyperinsulinism is transient and will spontaneously resolve at 1 month of age. Beckwith–Wiedemann syndrome is a congenital overgrowth syndrome, with hyperinsulinism caused by beta-cell hyperplasia.

Pathophysiology. Hyperinsulinism is due to unregulated insulin release from either the entire pancreas (diffuse beta-cell hyperfunction) or confined areas of the pancreas (focal adenomatous islet-cell hyperplasia). Insulin lowers circulating glucose, suppressing lipolysis and ketogenesis and decreasing the availability of free fatty acids and ketone bodies. Since these are alternative energy substrates for the brain during hypoglycemia, hyperinsulinemia places the infant at risk of severe neurologic dysfunction and seizures as consequences of neuroglycopenia.

Clinical Manifestations. Most infants with congenital hyperinsulinism present within the first postnatal days. Generally, they are born at term and are normal or large for gestational age. Many are macrosomic with a characteristic facial appearance. Neonates with Beckwith–Wiedemann syndrome present with a constellation of findings including macroglossia, abdominal wall defects, Wilms' tumors, renal abnormalities, and facial nevus.

Diagnosis. Congenital hyperinsulinism is recognized by severe hypoglycemia with an insulin level that is inappropriate to the level of blood glucose that is present (e.g., insulin level >5 U/mL with a plasma glucose level <50 mg/dL).

Diagnostic criteria are a high glucose requirement (>6–8 mg/kg/minute) needed to maintain normoglycemia, low serum blood glucose by laboratory analysis, measurable insulin, raised C-peptide, low free fatty acids, and low ketone body concentrations. Blood sampling must take place during hypoglycemia to be of diagnostic value (Werny et al., 2018). The administration of glucagon during hypoglycemia results in a glycemic response.

Management. The cornerstones of management are a high caloric intake and pharmacologic therapy to inhibit insulin secretion by the pancreas. A central venous catheter is required for reliable and safe administration of high glucose infusates during the acute phase. **Quality and Safety: Glucose infusion rates of 10 to 15 mg/kg/minute or higher may be required, and the rate of glucose necessary to maintain normoglycemia (fasting blood glucose >70 mg/dL)** is an indicator of the severity of the disease (Arnoux et al., 2011). Drugs include diazoxide, which inhibits insulin secretion by blocking the sulfonylurea receptor of the beta-cell, and octreotide, which is a somatostatin analogue. Diazoxide must be used with caution in the presence of hyperbilirubinemia because it is highly protein bound and will displace bilirubin from albumin binding sites. Glucagon to mobilize hepatic glucose can be added if needed as a short-term adjunct to therapy (Arnoux et al., 2011).

Unfortunately, the responsiveness of infants with hyperinsulinism to these agents is inconsistent and variable. Babies who do not show an adequate and immediate response may require pancreatectomy to prevent recurrent neuroglycopenia. Preoperative localization procedures and intraoperative biopsies will determine the exact nature of the lesion and how much of the pancreas must be removed. Focal disease may require only a partial pancreatectomy, but a near-total (>95%) removal of the pancreas is indicated for diffuse congenital hyperinsulinism. Loss of the pancreas can pose additional risks such as pancreatic insufficiency and diabetes mellitus.

Cystic Fibrosis

CF is an autosomal recessive disorder caused by mutations in the gene encoding for the CF transmembrane conductance regulator (CFTR) protein, of which more than 1,500 have been identified (O'Sullivan & Freedman, 2009). Data from newborn screening programs in the United States reveal that CF occurs in 1 in 3,000 White and 1 in 15,000 to 20,000 Blacks (Walters & Mehta, 2007).

Pathophysiology. Mutations in the *CFTR* gene affect the cyclic adenosine-5'-monophosphate (AMP)-mediated signals that stimulate chloride conductance in the epithelial cells of the exocrine ducts. Deficient chloride transport and the associated water transport abnormalities result in the production of abnormally viscid mucus. Nearly all organs and systems of the

body are affected, including the lungs and upper respiratory tract, gastrointestinal tract, pancreas, liver, sweat glands, and genitourinary tract. In the neonate, hyperviscous secretions in the intestines and a deficiency of pancreatic enzymes can combine to create a sticky plug of meconium, a condition known as *meconium ileus*. The meconium has a higher protein and lower carbohydrate concentration, making it more viscid than normal meconium.

Clinical Manifestations. Without a family history or prenatal screening, CF is not recognized at the time of birth in most affected neonates unless a meconium ileus is present. A simple meconium ileus is usually identified at 24 to 48 hours of age (occasionally earlier) when there are signs of intestinal obstruction: abdominal distension, bilious vomiting, and either failure to pass meconium or passage of gray-colored stools. On examination, the dilated loops of bowel have a doughy character that indent on palpation. A complicated meconium ileus has a more dramatic presentation with severe abdominal distension, signs of peritonitis such as tenderness, erythema, and clinical evidence of sepsis. The neonate may be acutely ill and require urgent surgical attention. Although not always present in the neonatal period, most patients with CF have pancreatic enzyme insufficiency and present with digestive symptoms or failure to thrive early in life. Other neonatal signs and symptoms include intestinal atresia, prolonged jaundice, and abdominal or scrotal calcifications (O'Sullivan & Freedman, 2009).

Diagnosis. The possibility of CF is raised in the neonate with meconium ileus, and the diagnosis can be confirmed with DNA testing. A sweat test can also be performed after the first 48 hours of life, if the infant is not edematous. A sweat test uses electrical-chemical stimulation of the skin to induce sweat, which is collected and analyzed for chloride content. Newborn screening for CF can be accomplished by measuring immunoreactive trypsinogen in dried blood samples. Screening for CF is now universally conducted in all 50 states and the District of Columbia (Wagener, Zemanick, & Sontag, 2012). Sometimes a meconium ileus is identified on prenatal ultrasound as a hyperechoic mass in the terminal ileum, representing thickened or dried meconium, and dilated bowel loops. Postnatal abdominal radiographs show unevenly dilated bowel and, occasionally, a characteristic "soap bubble" pattern, or small bubbles of gas that are caused by air mixing with the tenacious meconium.

Management. A meconium ileus requires prompt attention to prevent complications such as volvulus, bowel necrosis, or intestinal perforation. Treatment for simple meconium ileus is a therapeutic Gastrografin (Diatrizoate Meglumine) enema performed under fluoroscopy. Gastrografin is a hyperosmolar, radiopaque solution that evacuates the dried or thickened meconium from the intestine. Gastrografin is not used in infants with evidence of volvulus, gangrene, perforation, peritonitis, or atresia of the small bowel. The risks of the procedure are ischemia, hypovolemic shock, and perforation. It is essential to provide adequate hydration to compensate for the rapid fluid losses that can occur with the Gastrografin enema. It usually takes 24 to 48 hours to evacuate the softened meconium, and serial radiographs are usually ordered to monitor the evacuation. Feedings are started when signs of obstruction have subsided. **Quality and Safety: An infant who has undergone a Gastrografin enema should be observed closely for at least 48 hours for signs and symptoms of perforation of the bowel; late perforation is a rare but possible complication as long as 48 hours after the procedure.**

CF is also managed with a diet high in energy and fat to compensate for malabsorption and the increased energy demand of chronic inflammation. In addition to vitamin and mineral supplementation, a hydrolyzed protein formula containing medium-chain triglycerides is used. Medium-chain triglycerides do not require digestion by pancreatic enzymes for absorption. Pancreatic enzyme supplements are also needed to improve fat absorption. Meticulous care of the perianal area must be taken because these enzymes can cause severe perianal dermatitis. Breastfeeding has been shown to have significant benefits for infants with CF, although growth might be slightly slower, and should be encouraged (Wagener et al., 2012).

Infants can also develop early pulmonary infections with *Staphylococcus aureus* followed often by *Pseudomonas aeruginosa* (Wagener et al., 2012). Newer, promising therapies for the pulmonary complications of CF are currently under study. One of these is inhaled hypertonic saline, which draws water into the airways, rehydrating the periciliary layer and improving mucociliary clearance (O'Sullivan & Freedman, 2009).

Finally, of utmost importance, the care of the neonate with CF requires a team approach, in order to provide the family with the necessary resources and anticipatory guidance to manage this disorder and prevent complications for the best possible outcome (Box 10.2).

Box 10.2

NURSING IMPLICATIONS OF INFANTS WITH ENDOCRINE DISORDERS

Nurses should support the families of these infants in the following ways:

1. Assuring that the programs are implemented safely and effectively
2. Facilitating education of the nursing workforce and developing and contributing to programs of research focused on endocrine disorders
3. Educating parents with appropriately timed discussion of results
4. Parental teaching that includes materials that provide descriptions and results that will be communicated to the family and what they should expect if further testing is needed (Arnold et al., 2006; Davis et al., 2006)

SUMMARY

Some neonatal endocrine disorders are quite rare, and recognizing them requires a high index of suspicion. In recent years, neonatal screening programs have permitted the presymptomatic diagnosis of some of these disorders. This has led to earlier treatment and reduced morbidity, although most endocrine disorders still imply lifelong therapy for the affected infant.

CASE STUDY

■ **Identification of the Problem.** A 34-week gestation, 1.33-kg male infant was admitted to the NICU for small size and prematurity. Admission vital signs were HR 128, RR 72, BP 42/23 (mean 30), and axillary temperature 97.4°F. Blood glucose screen (point of care) was 104.

A peripheral IV was started with D10W at 80 mL/kg/day (GIR 5.5 mg/kg/minute), and the infant was made NPO. A repeat blood glucose screen on D10W was 545. In the belief that this was an error, it was repeated, and the result was 550. A serum glucose level

was drawn, and the IV fluids were changed to D5W. The serum glucose was 535. The initial D10W fluid bag was sent to the lab for analysis.

A repeat blood glucose screen on D5W was 550 (serum 632). IV fluids were changed to normal saline, and the repeat blood glucose was 443 (serum 635). An insulin drip was started at 0.05 U/kg/hour and titrated to maintain blood glucose level less than 250.

■ **Assessment: History and Physical Examination.** The infant was born by cesarean section to a 25-year-old G1 P0 mother following a pregnancy complicated by oligohydramnios. Apgar scores were 7 and 9 and the arterial cord pH was 7.27. Length was 38.5 cm, and head circumference 28 cm, placing him below the 10th percentile for all growth parameters.

Arterial blood gas taken in room air: pH 7.30, P_{CO_2} 35, P_{O_2} 128, base excess −7.7

Following this, 10 mL/kg of normal saline was given for metabolic acidosis.

Examination revealed a small but healthy-appearing male infant, without evidence of respiratory distress.

■ **Differential Diagnosis.** The initial suspected "diagnosis" for the extremely elevated blood glucose in this case was operator error; when the same result was obtained with a repeat specimen and confirmed by serum glucose, it was still viewed with a high degree of suspicion and the intravenous fluids were sent to the laboratory for analysis. The differential diagnosis of hyperglycemia in neonates includes iatrogenic causes, poor insulin sensitivity of the very-low-birth-weight or growth-restricted infant, sepsis, pancreatic agenesis, insulin resistance, TNDM or PNDM, and side effects of medications such as glucocorticoids and theophylline. Several of these were ruled out as they did not apply (the infant was not extremely premature, nor had he received any medications known to cause blood glucose elevation). Furthermore, the problem persisted after changing the IV fluids, ruling out an iatrogenic cause. Insulin resistance was ruled out because the infant responded promptly to an infusion of insulin. He did show evidence of intrauterine growth restriction but it was believed more likely that this was a consequence, rather than a cause, of his primary problem.

■ **Diagnostic Tests.** The following tests were ordered to further hone in on the cause of hyperglycemia:

- CBC: Hct 42%; WBC 4.4; Segs 20; Bands 8; platelets 274,000
- Blood cultures were negative at 24 and 48 hours
- Abdominal ultrasound (to rule out pancreatic agenesis): the organ appeared normal
- Insulin autoantibodies were negative; the insulin drip was stopped for 2 hours and insulin and C-peptide levels were drawn
- RESULTS: insulin level less than 2 mIU/mL
- C-peptide less than 0.5 ng/mL (reference range 0.8–3.1 ng/mL)
- Concurrent plasma glucose was 412

■ **Working Diagnosis.** The infant's presentation at birth and clinical course were most consistent with a diagnosis of NDM. He was intrauterine growth restricted, indicating a prenatal onset of the condition, and he had a mild metabolic acidosis. He had no evidence of autoimmune or structural pancreatic disease. He did not have septicemia or evidence of other infection. Furthermore, his laboratory studies revealed severe insulinopenia. The low level of C-peptide, a single-chain amino acid normally released with insulin in equal amounts, supports this diagnosis. It was not known whether his NDM was transient or permanent; this would require molecular genetic analysis, a test that was not done during the initial hospitalization.

■ **Development of Management Plan.** The management plan was to reintroduce glucose while continuing the insulin infusion, advancing to total parental nutrition as tolerated. Glucose levels would be monitored at least every 2 hours, with the goal of keeping the blood glucose less than 250. The plan included the introduction of feedings as early as feasible to improve control of blood glucose. Continuous insulin would be weaned as tolerated. If his diabetes showed no signs of resolution, subcutaneous insulin would be started for long-term management. The infant would continue to be followed by the pediatric endocrinologist.

■ **Implementation and Evaluation of Effectiveness.** Over the first few days, stabilization of the blood glucose level proved difficult. On total parenteral nutrition (TPN), the infant fluctuated between hyperglycemia and hypoglycemia. Feedings were introduced and this provided a measure of stability, although weight gain remained slow. The infant was eventually successfully managed with and discharged on subcutaneous insulin.

EVIDENCE-BASED PRACTICE BOX

Upon newborn screening, at least one of two extremely low gestational age neonates (24–28 weeks gestation) is found to have low serum thyroxine (T_4) levels. This condition is known as hypothyroxinemia of prematurity and is believed to be a transient maladaptation of physiology that reflects both immaturity and the effects of illness and treatments for other neonatal problems (La Gamma & Paneth, 2012). Both researchers and clinicians, however, have been uncertain about whether to treat hypothyroxinemia in these infants, or adopt a "watchful waiting" approach.

The concern about not treating these low T_4 levels is that thyroid hormones are known to be critical to normal brain development. With the loss of maternal sources of thyroid hormone, low T_4 levels exist at a vulnerable period of brain development. Evidence suggests that hypothyroxinemia of prematurity is associated with both cognitive and neurological delays (La Gamma, 2008). Therefore, studies have attempted to determine whether thyroid hormone supplementation would improve neurodevelopmental outcomes in low gestational age neonates. One such study, the largest interventional trial to date, tested the effects of a daily dose of 8 mg/kg of T_4 for 42 days, compared with placebo (van Wassenaer et al., 1997). On follow-up testing, an 18-point improvement in IQ scores was found in mental development at 2 years of age, and there

(*continued*)

EVIDENCE-BASED PRACTICE BOX (*continued*)

was an improvement in neurological outcomes in a subgroup of the most immature infants, less than 27 weeks gestation. At 5.5 and 10 years of follow-up, the benefits of T_4 supplementation continued for this subgroup, but for more mature infants, the reverse was true (Briët et al., 2001; van Wassenaer, Westera, Houtzager, & Kok, 2005).

Against a backdrop of this evidence, researchers undertook a study of four different thyroid regimens for neonates less than 28 weeks gestation diagnosed with hypothyroxinemia of prematurity (La Gamma et al., 2009). The key difference between this and previous trials was that this study aimed to maintain "biochemical euthyroidism" by reducing suppression of TSH. In previous trials, thyroid supplementation had resulted in a suppression of TSH levels. La Gamma et al. found evidence of clinical benefit (shorter duration of mechanical ventilation, lower rates of retinopathy of prematurity, and less necrotizing enterocolitis) with a *continuous* regimen of 4 mcg/kg/day for 42 days rather than a single daily supplement. This regimen raised total T_4 levels with only modest suppression of TSH.

As a result of this trial, study authors recommend T_4 replacement of 4 mcg/kg/day for 42 days, to achieve "biochemical euthyroidism," defined as a minimum free T_4 level of 1.5 ng/dL, a minimum total T_4 level of 6 mg/dL, a minimum total T_3 level of 52 ng/dL, and minimal suppression of TSH level (<0.4 mIU/L; La Gamma et al., 2009). Continuous infusion of T_4 is believed to more closely approximate normal physiology by achieving a sustained elevation in total T_4. Iodide supplementation (30 mg/kg/day orally) is also essential. Only a randomized, placebo-controlled clinical trial can provide evidence of long-term neurodevelopmental improvement associated with this regimen. In the absence of such evidence, clinicians may remain reluctant to adopt a new standard of care.

References

Briët, J. M., van Wassenaer, A. G., Dekker, F. W., de Vijlder, J. J., van Baar, A., & Kok, J. H. (2001). Neonatal thyroxine supplementation in very preterm children: Developmental outcome evaluated at early school age. *Pediatrics, 107*, 712–718. doi:10.1542/peds.107.4.712

La Gamma, E. F. (Ed.). (2008). Transient hypothyroxinemia of prematurity: 10 reports from our group. *Seminars in Perinatology, 32*, 377–446. Retrieved from https://www.sciencedirect.com/journal/seminars-in-perinatology/vol/32/issue/6

La Gamma, E. F., & Paneth, N. (2012). Clinical importance of hypothyroxinemia in the preterm infant and a discussion of treatment concerns. *Current Opinion in Pediatrics, 24*, 172–180. doi:10.1097/MOP.0b013e32835067cc

La Gamma, E. F., van Wassenaer, A. G., Ares, S., Golombek, S. G., Kok, J. H., Quero, J., . . . Paneth, N. (2009). Phase 1 trial of 4 thyroid hormone regimens for transient hypothyroxinemia in neonates of <28 weeks' gestation. *Pediatrics, 124*, e258–e268. doi:10.1542/peds.2008-2837

van Wassenaer, A. G., Kok, J. H., de Vijlder, J. J., Briët, J. M., Smit, B. J., Tamminga, P., . . . Vulsma, T. (1997). Effects of thyroxine supplementation on neurologic development in infants born at less than 30 weeks' gestation. *New England Journal of Medicine, 336*, 21–26. doi:10.1056/NEJM199701023360104

van Wassenaer, A. G., Westera, J., Houtzager, B. A., & Kok, J. H. (2005). Ten-year follow-up of children born at <30 weeks' gestational age supplemented with thyroxine in the neonatal period in a randomized, controlled trial. *Pediatrics, 116*, e613–e618. doi:10.1542/peds.2005-0876

ONLINE RESOURCES

The Endocrine Society. Retrieved from http://www.endo-society.org

List of disorders included in newborn screening programs. Retrieved from Wikipedia

National Newborn Screening and Global Resource Center. Retrieved from http://genes-r-us.uthscsa.edu

NORD National Organization for Rare Disease https://rarediseases.org

Orphanet. Retrieved from http://www.orpha.net/consor/cgi-bin/index.php

Pediatric Endocrine Society. Retrieved from http://www.lwpes.org

Pediatric Endocrinology and Inborn Errors of ... - AccessPediatrics https://accesspediatrics.mhmedical.com/book.aspx?bookID=2042

Schulze, A, Lindner, M, Kohnmuleer, D, Ogemoller, K, Mayatepek, E, Hoffman, GF. Expanded Newborn Screening for Iinborn Errors of Metabolism by electrspray Ionization Tandem Mass Sectrometry: Results, outcome and Implications. *Pediatrics, 2003. 111* (6 pt 1): 1399–1406.

REFERENCES

Alatzoglou, K. S., & Dattani, M. T. (2009). Genetic forms of hypopituitarism and their manifestation in the neonatal period. *Early Human Development, 85*, 705–712. doi:10.1016/j.earlhumdev.2009.08.057

Allen, L. (2009). Disorders of sexual development. *Obstetrics and Gynecological Clinics of North America, 36*, 25–45. doi:10.1016/j.ogc.2009.02.001

Arnold, C. L., Davis, T. C., Frempong, J. O., Humiston, S. G., Bocchini, A., Kennen, E. M., & Lloyd-Puryear, M. (2006). Assessment of newborn screening parent education materials. *Pediatrics, 117*(Suppl. 3), S320–S325.

Arnoux, J.-B., Verkarre, V., Saint-Martin, C., Montravers, F., Brassier, A., Valayannopoulos, V., . . . de Lonlay, P. (2011). Congenital hyperinsulinism: Current trends in diagnosis and therapy. *Orphanet Journal of Rare Diseases, 6*, 63. doi:10.1186/1750-1172-6-63

Auchus, R. H., Witchel, S. F., Leight, K. R., Aisenberg, J., Azziz, R., Bachega, T. A., . . . Zuckerman, A. E. (2010). Guidelines for the development of comprehensive care centers for congenital adrenal hyperplasia: Guidance from the CARES Foundation Initiative. *International Journal of Pediatric Endocrinology, 2010*, 275213. doi:10.1155/2010/275213

Askenazi, D., Selewski, D., Willig, L., & Warady, B. A. (2018). Acute kidney injury and chronic kidney disease. In C. A. Gleason & S. E. Juul (Eds.), *Avery's diseases of the newborn* (10th ed., pp. 1280–1300). Philadelphia, PA: Elsevier.

Bethin, K., & Fuqua, J. S. (2014). General concepts and physiology. In M. S. Kappy, D. B. Allen, & M. E. Geffner (Eds.), *Pediatric practice: Endocrinology* (2nd ed., pp. 1–26). New York, NY: McGraw-Hill.

Brown, J., & Warne, G. (2005). Practical management of the intersex infant. *Journal of Pediatric Endocrinology and Metabolism, 18*, 3–23. doi:10.1515/jpem.2005.18.1.3

Davis, T. C., Humiston, S. G., Arnold, C. L., Bocchini, J. A. Jr., Bass III, P. F., Kennen, E. M., . . . Lloyd-Puryear, M. (2006). Recommendations for effective newborn screening communication: Results of focus groups with parents, providers, and experts. *Pediatrics, 117*(Suppl. 3), S326–S340.

Divall, S. A., & Merjaneh, L. (2018). Developmental endocrinology. In C. A. Gleason & S. E. Juul (Eds.), *Avery's diseases of the newborn* (10th ed., p. 1324–1332). Philadelphia, PA: Elsevier.

Edghill, E. L., Flanagan, S. E., & Ellard, S. (2010). Permanent neonatal diabetes due to activating mutations in *ABCC8* and *KCNJ11*. *Reviews in Endocrine and Metabolic Disorders, 11*, 193–198. doi:10.1007/s11154-010-9149-x

Escobar, O., Viswanathan, P., & Witchel, S. F. (2018). Pediatric endocrinology. In B. J. Zitelli, S. McIntire, & A. J. Nowalk (Eds.), *Atlas of pediatric physical diagnosis* (7th ed., pp. 341–377). Philadelphia, PA: Elsevier.

Fechner, P. Y. (2018). Disorders of the adrenal gland. In C. A. Gleason & S. E. Juul (Eds.), *Avery's diseases of the newborn* (10th ed., pp. 1351–1364). Philadelphia, PA: Elsevier.

Greeley, S. A., John, P. M., Winn, A. N., Ornelas, J., Lipton, R. B., Philipson, L. H., Bell, G. I., & Huang, E. S. (2011). The cost-effectiveness of personalized genetic medicine: The case of genetic testing in neonatal diabetes. *Diabetes Care, 34*, 622–627. doi:10.2337/dc10-1616

Grulich-Henn, J., Wagner, V., Thon, A., Schober, E., Marg, W., Kapellen, T. M., . . . Holl, R. W. (2010). Entities and frequency of neonatal diabetes: Data from the diabetes documentation and quality management system (DVP). *Diabetic Medicine, 27*, 709–712. doi:10.1111/j.1464-5491.2010.02965.x

Hawdon, J. M. (2011). Babies born after diabetes in pregnancy: What are the short- and long-term risks and how can we minimise them? *Best Practice and Research Clinical Obstetrics and Gynaecology, 25*, 91–104. doi:10.1016/j.bpobgyn.2010.10.005

Hay, W. W., Jr. (2012). Care of the infant of the diabetic mother. *Current Diabetes Reports, 12*, 4–15. doi:10.1007/s11892-011-0243-6

Homko, C. J. (2010). Gestational diabetes mellitus: Can we reach consensus? *Current Diabetes Reports, 10*, 252–254. doi:10.1007/s11892-010-0117-3

Houk, C. P., Baskin, L. S., & Levitsky, L. L. (2019). Management of the infant with atypical genitalia (disorder of sex development). In A. G. Hoppin (Ed.), *UpToDate*. Retrieved from https://www.uptodate.com/contents/management-of-the-infant-with-atypical-genitalia-disorder-of-sex-development

Houk, C. P., & Lee, P. A. (2005). Intersexed states: Diagnosis and management. *Endocrinology and Metabolism Clinics of North America, 34*, 791–810. doi:10.1016/j.ecl.2005.04.014

Houk, C. P., & Lee, P. A. (2012). Update on disorders of sex development. *Current Opinion in Endocrinology, Diabetes, and Obesity, 19*, 28–32. doi:10.1097/med.0b013e32834edacb

Hyman, S. J., Novoa, Y., & Holzman, I. (2011). Perinatal endocrinology: Common endocrine disorders in the sick and premature newborn. *Pediatric Clinics of North America, 58*, 1083–1098. doi:10.1016/j.pcl.2011.07.003

Intersex Society of North America Consortium on the Management of Disorders of Sex Development. (2006). *Clinical guidelines for the management of disorders of sex development in childhood*. Retrieved from http://www.dsdguidelines.org/files/clinical.pdf

Kim, G., Nandi-Munshi, D., & DiBlasi, C. (2018). Disorders of the thyroid gland. In C. A. Gleason & S. E. Juul (Eds.), *Avery's diseases of the newborn* (10th ed., pp. 1388–1402). Philadelphia, PA: Elsevier Saunders.

Köhler, B., Lumbroso, S., Leger, J., Audran, F., Grau, E. S., Kurtz, F., . . . Sultan, C. (2005). Androgen insensitivity syndrome: Somatic mosaicism of the androgen receptor in seven families and consequences for sex assignment and genetic counseling. *Journal of Clinical Endocrinology and Metabolism, 90*, 106–111. doi:10.1210/jc.2004-0462

La Gamma, E. F., & Paneth, N. (2012). Clinical importance of hypothyroxinemia in the preterm infant and a discussion of treatment concerns. *Current Opinion in Pediatrics, 2*, 172–180. doi:10.1097/mop.0b013e32835067cc

La Gamma, E. F., van Wassenaer, A. G., Ares, S., Golombek, S. G., Kok, J. H., Quero, J., . . . Paneth, N. (2009). Phase 1 trial of 4 thyroid hormone regimens for transient hypothyroxinemia in neonates of <28 weeks' gestation. *Pediatrics, 124*, e258–e268. doi:10.1542/peds.2008-2837

Lee, P. A., Houk, C. P., Ahmed, S. F., & Hughes, I. A. (2006). Consensus statement on management of intersex disorders. *Pediatrics, 118*, e488–e500. doi:10.1542/peds.2006-0738

Misra, M., & Lee, M. M. (2005). Intersex disorders. In T. Moshang (Ed.), *Pediatric endocrinology*. St. Louis, MO: Elsevier.

Mitchell, M. L., Hsu, H.-W., Sahai, I., & Massachusetts Pediatric Endocrine Workgroup. (2011). The increased incidence of congenital hypothyroidism: Fact or fancy? *Clinical Endocrinology, 75*, 806–810. doi:10.1111/j.1365-2265.2011.04128.x

Modi, N. (2012). Fluids, electrolytes, renal function, and acid–base balance. In A. Y. Elzouki, F. B. Stapleton, R. J. Whitley, W. Oh, H. A. Harfi, & H. Nazer (Eds.), *Textbook of clinical pediatrics* (p. 256). Berlin, Germany: Springer Verlag.

Morel, Y., Rey, R., Teinturier, C., Nicolino, M., Michel-Calemard, L., Mowszowicz, I., . . . Josso, N. (2002). Aetiological diagnosis of male sex ambiguity: A collaborative study. *European Journal of Pediatrics, 161*, 49–59. doi:10.1007/s00431-001-0854-z

Mutlu, M., Karagüzel, G., Aslan, Y., Cansu, A., & Ökten, A. (2011). Adrenal hemorrhage in newborns: A retrospective study. *World Journal of Pediatrics, 7*, 355–357. doi:10.1007/s12519-011-0259-7

Ng, P. C. (2011). Effect of stress on the hypothalamic-pituitary-adrenal axis in the fetus and newborn. *Journal of Pediatrics, 158*(Suppl. 2), e41–e43. doi:10.1016/j.jpeds.2010.11.012

Öçal, G. (2011). Current concepts in disorders of sexual development. *Journal of Clinical Research in Pediatric Endocrinology, 3*, 105–114. doi:10.4274/jcrpe.v3i3.22

Ogilvy-Stuart, A. L., & Brain, C. E. (2004). Early assessment of ambiguous genitalia. *Archives of Disease in Childhood, 89*, 401–407. doi:10.1136/adc.2002.011312

Osborn, D. A., & Hunt, R. W. (2007). Prophylactic postnatal thyroid hormones for prevention of morbidity and mortality in preterm infants. *Cochrane Database of Systematic Reviews, 24*, CD005948. doi:10.1002/14651858.cd005948

O'Sullivan, B. P., & Freedman, S. D. (2009). Cystic fibrosis. *Lancet, 373*, 1891–1904. doi:10.1016/s0140-6736(09)60327-5

Pass, K. A., & Neto, E. C. (2011). Update: Newborn screening for endocrinopathies. *Endocrinology and Metabolism Clinics of North America, 38*, 827–837. doi:10.1016/j.ecl.2009.08.005

Polak, M., Refetoff, S., Szinnai, G., & Van Vliet, G. (2017). Disorders of the thyroid gland. In K. Sarafoglou, G. F. Hoffmann, & K. S. Roth (Eds.), *Pediatric endocrinology and inborn errors of metabolism* (2nd ed., pp. 481–512). New York, NY: McGraw-Hill.

Rastogi, M. V., & LaFranchi, S. H. (2010). Congenital hypothyroidism. *Orphanet Journal of Rare Diseases, 5*, 17. doi:10.1186/1750-1172-5-17

Richardson, K., & Yonekawa, K. (2018). Glomerulonephropathies and disorders of tubular function. In C. A. Gleason & S. E. Juul (Eds.), *Avery's diseases of the newborn* (10th ed., pp. 1301–1307). Philadelphia, PA: Elsevier.

Seki, Y., Williams, L., Vuguin, P. M., & Charron, M. J. (2012). Minireview: Epigenetic programming of diabetes and obesity: Animal models. *Endocrinology, 153*, 1031–1038. doi:10.1210/en.2011-1805

Shnorhavorian, M., & Fechner, P. Y. (2018). Disorders of sexual differentiation. In C. A. Gleason & S. E. Juul (Eds.), *Avery's diseases of the newborn* (10th ed., pp. 1365–1387). Philadelphia, PA: Elsevier.

Simpser, T., & Rapaport, R. (2010). Update on some aspects of neonatal thyroid disease. *Journal of Clinical Research in Pediatric Endocrinology, 2*, 95–99. doi:10.4274/jcrpe.v2i3.95

Speiser, P. W., Azziz, R., Baskin, L. S., Ghizzoni, L., Hensle, T. W., Merke, D. P., . . . Endocrine Society. (2010). Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: An Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism, 95*, 4133–4160. doi:10.1210/jc.2009-2631

Sperling, M. A. (2006). The genetic basis of neonatal diabetes mellitus. *Pediatric Endocrinology, 4*(Suppl. 1), 71–75.

Srinivasan, R., Harigopal, S., Turner, S., & Cheetham, T. (2012). Permanent and transient congenital hypothyroidism in preterm infants. *Acta Paediatrica, 101*, e179–e182. doi:10.1111/j.1651-2227.2011.02536.x

Srivatsa, A., Majzoub, J. A., & Kappy, M. S. (2014). Posterior pituitary and disorders of water metabolism. In M. S. Kappy, D. B. Allen, & M. E. Geffner (Eds.), *Pediatric practice: Endocrinology* (2nd ed., pp. 321–350). New York, NY: McGraw-Hill.

Stokowski, L. (2015). Endocrine disorders. In M. T. Verklan & M. Walden (Eds.), *Core curriculum for neonatal intensive care nursing* (5th ed., pp. 632–661). Philadelphia, PA: Elsevier.

Tenore, A., & Driul, D. (2009). Genomics in pediatric endocrinology—Genetic disorders and new techniques. *Endocrinology and Metabolism Clinics of North America, 38*, 471–490. doi:10.1016/j.ecl.2009.06.001

Thyen, U., Richter-Appelt, H., Wiesemann, C., Holterhus, P. M., & Hiort, O. (2005). Deciding on gender in children with intersex conditions. *Treatments in Endocrinology, 4*, 1–8. doi:10.2165/00024677-200504010-00001

Tuladhar, R., Davis, P. G., Batch, J., & Doyle, L. W. (1998). Establishment of a normal range of penile length in preterm infants. *Journal of Paediatric and Child Health, 35*, 471–473. doi:10.1046/j.1440-1754.1998.00278.x

van Wassenaer, A. G., & Kok, J. H. (2004). Hypothyroxinaemia and thyroid function after preterm birth. *Seminars in Neonatology, 9*, 3–11. doi:10.1016/s1084-2756(03)00114-3

Wagener, J. S., Zemanick, E. T., & Sontag, M. K. (2012). Newborn screening for cystic fibrosis. *Current Opinion in Pediatrics, 15*(3), 309–315. doi:10.1097/00008480-200306000-00015

Walsh, J. M., Mahony, R., Byrne, J., Foley, M., & McAuliffe, F. M. (2011). The association of maternal and fetal glucose homeostasis with fetal adiposity and birthweight. *European Journal of Obstetrics, Gynecology and Reproductive Biology, 159*, 338–341. doi:10.1016/j.ejogrb.2011.09.022

Walters, S., & Mehta, A. (2007). Epidemiology of cystic fibrosis. In M. Hodson, D. M. Geddes, & A. Bush (Eds.), *Cystic fibrosis* (3rd ed., pp. 21–45). London, England: Edward Arnold.

Werny, D., Taplin, C., Bennett, J. T., & Pihoker, C. (2018). Disorders of carbohydrate metabolism. In C. A. Gleason & S. E. Jull (Eds.), *Avery's diseases of the newborn* (10th ed., pp. 1403–1416). Philadelphia, PA: Elsevier.

Witchel, S. F., & Azziz, R. (2011). Congenital adrenal hyperplasia. *Journal of Pediatric and Adolescent Gynecology, 24*, 116–126. doi:10.1016/j.jpag.2010.10.001

CHAPTER 11

Immune System

Mary Beth Bodin and Jacqueline Hoffman

INTRODUCTION

Despite all the lessons we have learned, neonatal sepsis continues to be a leading cause of neonatal and infant morbidity and mortality. The intact uterine environment helps to protect the fetus from a variety of pathogens including bacteria, viruses, fungi, protozoa, and parasites. Although there is protection, breaches do occur and this protection is not absolute. The birth canal may not be a sterile environment as once thought. New evidence has shown the presence of microbiota in the placenta and amniotic fluid in asymptomatic term pregnancies (Chu et al., 2016). The newborn is exposed to a wide variety of microorganisms during labor and delivery and in the event of ruptured membranes. The extrauterine environment exposes the infant to even more potential pathogens.

To understand and appreciate the challenges infants face in the first few days and weeks of life, it is necessary to review the basics of innate and adaptive immunity and potential alterations to the neonatal immune system. This chapter will discuss development of the immune system and will describe assessment parameters for evaluating the infant with suspected and culture-proven infection as well as diagnostic measures and treatment for the most common causes of newborn infection. Due to the importance of a broader approach to combating mortality from neonatal sepsis, a global perspective will be presented. The emergence of resistant organisms and the possible detrimental effects of prolonged antibiotic usage are becoming more influential in the treatment choices in individual units; therefore, the importance of antibiotic stewardship will be introduced. Detailed discussions on antibiotic stewardship and antibiotic resistance will be covered in another chapter in this text.

DEVELOPMENT OF THE IMMUNE SYSTEM

The overall goal of the immune system is to recognize foreign substances and activate systems to inactivate, destroy, and eliminate this material from the body. Immaturity of the immune system, seen especially in preterm infants, contributes to increased susceptibility to bacterial, viral, and fungal infections. The immune system consists of two separate defense mechanisms, the innate and adaptive subsystems. The innate system consists of external barriers such as the skin and mucous membranes, leukocytes and other defense cells, enzymes, and proteins in the blood. Natural killer cells are an important part of the innate immune system. These cells destroy invasive cells with cytotoxins. It is easy to see why this system is considered to be the first line of defense. The adaptive system takes over when the innate system fails. It may be delayed but is more accurate and efficient. This system produces memory cells; therefore, it is responsible for immunological memory. The adaptive immune system is composed of T lymphocytes, B lymphocytes, and antibodies (Simon, Hollander, & McMichael, 2015).

Innate Immune System

The innate or natural immune system is the first line of defense acting within minutes of initial exposure. This system does not require prior exposure to the pathogen to mount a response. This system consists of granulocytes (mainly neutrophils), antigen-presenting cells (monocytes), and natural killer cells. Neutrophils are the first phagocytic cell to reach the site of infection; sensing the foreign pathogen, neutrophils adhere to the vascular endothelium and migrate toward the site of infection to engulf and kill the pathogen. The response to the infectious process is to release more neutrophils from the storage pool, resulting in the release of more immature neutrophils as well as resulting in what is known as a left shift (a preponderance of immature to mature cells). The innate immune system utilizes toll-like receptors (expressed on monocytes), NOD (nucleotide-binding oligomerization domain)-like receptors, and RIG (retinoic acid-inducible gene)-like receptors to identify and respond to pathogen-associated molecular patterns resulting in the production of cytokines and proinflammatory responses, which activate the adaptive immune system (Camacho-Gonzalez, Spearman, & Stoll, 2013). In neonates, they have a decreased ability to produce proinflammatory cytokines, in particular tumor necrosis factor and interleukin (IL)-6. Neonates also have decreased neutrophil and dendritic cell functions, decreased adhesion ability, and decreased response to chemotactic factors affecting the ability to deform and penetrate the vascular endothelial lining (Basha, Surendran, & Pichichero, 2014; Camacho-Gonzalez et al., 2013). Finally, there is reduced cytokine production resulting in decreased activation of natural killer cells. All of these factors in the neonate place them at increased susceptibility to bacterial and viral infections (Camacho-Gonzalez et al., 2013).

Adaptive Immune System

The adaptive or acquired immune system relies on memory; this antigen-specific response is guided by recognition of prior exposure to pathogens. The adaptive immune system relies on T lymphocytes

and B lymphocytes. T lymphocytes provide cell-mediated immunity. They develop in the thymus and then circulate to the periphery. There are two different types of T lymphocytes: CD4 T cells and CD8 T cells. The CD4 T cells are "helper" cells that stimulate antibody production, whereas CD8 T cells act as cytotoxic killer cells. B lymphocytes provide humoral immunity. They develop in the bone marrow and circulate to the peripheral lymphatic system where they differentiate into plasma cells that secrete five types of immunoglobulins: immunoglobulin A (IgA), immunoglobulin D (IgD), immunoglobulin E (IgE), immunoglobulin G (IgG), and immunoglobulin M (IgM). The only immunoglobulin transplacentally transferred is IgG. The presence of IgM in the neonate at birth reflects a response to intrauterine infection exposure.

To minimize the overwhelming inflammatory response that would occur at the time of delivery from a relatively sterile environment, the adaptive immune system function increases slowly in the newborn. Skin and mucosal barriers in the preterm infant do not provide as effective barrier function as in the term and older neonate (Collins, Weitkamp, & Wynn, 2018). The neonate has decreased cytotoxic function as well as decreased memory, impacting the ability to respond effectively to infections (Camacho-Gonzalez et al., 2013).

The development of the immune system in the fetus and newborn cannot be studied in isolation from maternal influences. The ability of the mother's body to tolerate the fetus during pregnancy, rather than rejecting it as a foreign body, is not thoroughly understood. It is well documented that maternal blood with immunocompetent T lymphocytes circulates in contact with fetal cells, that both fetal and maternal cells are exchanged through the placenta, and that humoral and cellular immunity to fetal antigens develops in the mother. Recent studies have focused on maternal antibody transfer as it protects the newborn against infection prior to childhood immunizations and natural responses of the infant to infection. Secretory IgA in breast milk may also interfere with successful immunization, particularly with live poliovirus, by neutralization of virus by antibody in the gastrointestinal (GI) tract (Jennewein, Abu-Raya, Jiang, Alter, & Marchant, 2017; Maldonado, Nizet, Klein, Remington, & Wilson, 2016). Maternal placental transfer of IgG is inversely related to gestational age with minimal transfer in the first trimester and increases occur predominantly during the third trimester, leaving premature infants with a relative deficit (only 50% transfer by 32 weeks' gestation). Such immunity is transient; nevertheless, it may provide protection during a vulnerable time of life (Camacho-Gonzalez et al., 2013; Hong & Lewis, 2016). After birth, levels of IgG fall to their lowest levels between 2 and 4 months of age, which is referred to as physiologic or transient hypogammaglobulinemia. Infants do not begin producing their own IgG in response to exposure to pathogens until around 6 months of age. New and exciting evidence is available concerning the impact of the maternal microbiota on neonatal immune development. It is now recognized that maternal diet, including micronutrients, and the maternal microbiome significantly influence the neonatal innate and adaptive immune systems. It is known that the maternal gut and genital microbiota are transferred to the infant at birth and through the placental pathway (Jennewein et al., 2017).

Global Perspective on Neonatal Infection

The incidence of infection varies according to the level of perinatal care available, economic standards, and other perinatal risk factors in newborns, such as prematurity. Because the world is becoming smaller in terms of travel and involvement, it is no longer sufficient to concern ourselves with what is relevant to the North American continent. Our greatest concern is the challenge to eliminate the gaps in healthcare access and, therefore, to improve health outcomes worldwide. One of the barriers to understanding the overall burden of global neonatal infection is the general paucity of data from low- and middle-income countries (Fleischmann-Struzek et al., 2018). Although child and infant mortality appears to be declining globally, infant morbidity is not. Neonatal sepsis resulting in death accounts for 26% of all deaths in infants and children under 5 years of age worldwide with mortality the highest in sub-Saharan Africa (Ranjeva, Warf, & Schiff, 2018). A recent meta-analysis of population-based neonatal and pediatric data estimated neonatal mortality from sepsis at 11% to 19%. The authors identified that data from low-income countries were lacking due to not meeting inclusion criteria (Shane, Sanchez, & Stoll, 2017). In the United States, the incidence of culture-proven early-onset sepsis (EOS) is estimated to be 0.77 to 2 per 1,000 live births. The incidence and mortality in very low birthweight (VLBW) infants is even higher. In the United States, there is a large disparity in rates of infection and mortality with black infants, preterm especially, having the highest rates of sepsis and mortality at 5.14 per 1,000 live births (Anderson-Berry, Bellig, & Ohning, 2015; Simonsen, Anderson-Berry, Delair, & Daves, 2014). In those settings with the highest mortality (developing countries), neonatal infections may account for up to 50% of all neonatal deaths (Zaidi, Darmstadt, & Stoll, 2016). Improved knowledge and technology to care for less mature and smaller newborns have led to an increased population of newborns at higher risk for bacterial infection. Major complications of infection include respiratory distress, shock, acidosis, disseminated intravascular coagulation (DIC), and meningitis. Long-term morbidity remains a concerning consequence of neonatal infections.

ASSESSMENT AND MANAGEMENT OF THE INFANT WITH SUSPECTED OR PROVEN INFECTION

Host defense mechanisms begin to develop early in gestation; however, they remain immature and often do not function efficiently even in the term newborn. Although the neonate's immune system is not fully developed, the newborn is able to respond to the environment, resulting in certain markers that can be detected in lab studies such as the complete blood count (CBC) and the C-reactive protein (CRP). Even so, the infant's immature immune system is easily overwhelmed. The immaturity of the immune system is responsible for the relatively high prevalence of infectious disease during the neonatal period, as well as the occurrence of neonatal infection from microorganisms that do not generally cause infection in older individuals. The susceptibility to infectious processes and the associated high morbidity and mortality make early identification and treatment of infection in a newborn a critical component of care (Anderson-Berry et al., 2015).

Clinical Signs of Infection

Identifying and caring for a newborn with an infection can be one of the greatest challenges in nursing. Nurses are often the first to recognize that there is something "wrong" with an infant, and this often leads to investigation of the signs. Generally, treatment is begun once a presumptive diagnosis of infection is made because the benefits of early treatment most often outweigh the risks of unnecessary treatment. Signs and symptoms of neonatal sepsis are nonspecific and are often related to the specific organism responsible and may be attributable to other diseases or conditions such as respiratory distress syndrome, metabolic disorders, or stress from a difficult delivery. These other diagnoses must be ruled out while maintaining a high index of suspicion for sepsis. The most commonly recognized signs and symptoms of infection are listed

in Box 11.1. Temperature instability, hypothermia in particular, the inability of the neonate to maintain temperature in the normal range with rectal temperature less than or equal to 35°C (95°F) is a strong predictor for infection. Newborns traditionally do not have well-developed febrile mechanisms; therefore, the absence of fever does not indicate the absence of infection. Premature infants more often present with a low body temperature. Hyperthermia may occur in both bacterial and viral infections in term newborns, with rectal temperatures of greater than 100.4°F, but this is relatively rare in preterm infants. An infected infant may present with lethargy, poor feeding, decreased reflexes, abdominal distention, delayed gastric emptying time, and perhaps diarrhea or loose green or brown stools. Hypoglycemia or hyperglycemia, as well as glycosuria, may result from the inability to maintain normal metabolic processes and impaired glucose metabolism (Nizet & Klein, 2016).

Vascular perfusion is typically decreased; the infected neonate may appear gray, mottled, or ashen in color with poor perfusion, prolonged capillary filling time, and hypotension. Skin changes may also include cyanosis and petechiae. Thrombocytopenia is often present. Infections can cause DIC, resulting in altered prothrombin time, partial thromboplastin time, and split fibrin product laboratory values. Hemolytic anemia may occur as a part of the inflammatory process and this can significantly decrease oxygen-carrying capacity, especially in the preterm infant. Cardiovascular shock can be a sudden clinical sign of fulminant infection that requires immediate and aggressive intervention to restore adequate circulation. Unexplained bradycardia, sclerema, and sudden purpura, rash, or petechiae are other signs of systemic infection (Weinberg & D'Angio, 2016).

Apnea in a term (nonsedated) newborn in the first few hours of life should be considered a serious sign of inability to regulate the brain's respiratory center. Apnea in the first 24 hours of life in a preterm newborn is a common sign of infection. Respiratory distress can be an early sign of pneumonia and must be considered carefully. Jaundice, hepatosplenomegaly, and irritability may also be found in infants with infection. The wide variability of signs of infection warrants inclusion of infection as part of the differential diagnosis in any ill infant.

Risk Factors

Prematurity is the most prevalent risk factor for infection, as premature infants are far more susceptible to the invasion of foreign microorganisms. Preterm infants have decreased maternal antibodies (passive immunity). The maternal antibodies, developed by exposure to antigens and subsequent creation of an antibody defense system, provide temporary protection to the newborn, but preterm newborns are born before the majority of maternal antibodies are transferred from the maternal circulation. Also, the cellular immune system is not well developed in the preterm newborn; thus, there is decreased phagocytic cellular defenses.

Box 11.1

SIGNS AND SYMPTOMS OF NEONATAL INFECTION

Clinical

- General
- Poor feeding
- Irritability
- Lethargy
- Temperature instability

Skin

- Petechiae
- Pustulosis
- Sclerema
- Edema
- Jaundice

Respiratory

- Grunting
- Nasal flaring
- Intercostal retractions
- Tachypnea/apnea

Gastrointestinal

- Diarrhea
- Hematochezia
- Abdominal distention
- Emesis
- Aspirates

Central Nervous System

- Hypotonia
- Seizures
- Poor spontaneous movement

Circulatory

- Bradycardia/tachycardia
- Hypotension
- Cyanosis
- Decreased perfusion

Laboratory Values

White blood cell count

- Neutrophils
  <5,000 cells/mm^3, neutropenia
  >25,000 cells/mm^3, neutrophilia
- Absolute neutrophil count (neutrophil and bands)
  <1,800 cells/mm^3 (during first week)
- Immature: total neutrophil ratio
  >0:2
- Platelet count
  <100,000, thrombocytopenia

Cerebrospinal fluid (Results outside the normal ranges below suggest central nervous system infection.)

- Protein (normal values)
  150 to 200 mg/L (term)
  300 mg/L (preterm)
- Glucose (normal values)
  50% to 60% or more of blood glucose level

Note: Symptoms and values are based on over 30 years of practice and observation by the authors. Individual practices must rely on current literature for diagnosis and treatment plans.

Prolonged rupture of the fetal membranes (PROM) is a well-known risk factor for the development of infection. The fetus is at increased risk because the break in the amniotic sac provides a pathway for the migration of microorganisms up the vaginal vault to the fetus. Delaying delivery in a pregnancy in a mother with PROM and a preterm fetus until pulmonary maturity is achieved creates the potential environment for bacterial proliferation and subsequent newborn infection. The benefit in promoting maturity of the immature lungs is weighed against the risk of overwhelming infection in the baby. Development of pulmonary hypoplasia is another serious concern when delivery is delayed after premature prolonged rupture of membranes (ROM; Adams Waldorf, Gibbs, & Gravett, 2016). PROM, generally considered as ROM lasting longer than 18 hours, is considered a risk factor in the evaluation of infants for potential for infection (Jefferies, 2017; Leonard & Dobbs, 2015; Shah & Padbury, 2014).

Although the most common cause of maternal fever in labor is dehydration, a fever may indicate maternal infection. A mother with an infection before or during delivery may transmit it to the infant. If maternal temperature is greater than or equal to 100.4°F during labor, evaluation for infection in the newborn is warranted (Adams Waldorf et al., 2016). Maternal cervical or amniotic fluid cultures may identify the causative microorganism. If the maternal illness suggests viral infection, newborn viral cultures should be obtained. Early identification of causative agents in the mother may help in the management of the newborn by allowing faster identification of the microorganism and initiation of appropriate antimicrobial therapy.

Foul-smelling amniotic fluid is an indication for newborn antimicrobial therapy in symptomatic infants. Routine blood cultures and a CBC with differential are indicated as a screen for newborn infection. Under these circumstances, the placenta should be sent for pathologic evaluation. Other risk factors associated with newborn infection are antenatal or intrapartal asphyxia, iatrogenic complications of treatment, and invasive procedures.

Stress inhibits the ability to fight infection by increasing the metabolic rate, which requires more oxygen and energy. A severely compromised hypoxemic newborn may have regional tissue damage. Ischemic or necrotic areas in the lungs, heart, brain, or GI system promote colonization and overgrowth of normal bacterial flora. This overgrowth of bacteria is one of the most common sources of newborn infection. Tissue damage can be prevented or repaired only if the infectious process is reversed and adequate tissue perfusion is restored.

Several known maternal factors are associated with newborn infection: low socioeconomic status, malnutrition, inadequate prenatal care, substance abuse, premature or prolonged ROM, presence of a urinary tract infection at delivery, peripartum infection, clinical amnionitis, and general bacterial colonization. Newborn risk factors include antenatal stress, intrapartal stress (perinatal asphyxia), congenital anomalies, male sex, multiple gestations, concurrent neonatal disease processes, prematurity, immaturity of the immune system, invasive admission procedures, and antimicrobial therapies.

Diagnostic Workup

A high index of suspicion of infection, early identification of the microorganism, and institution of appropriate therapy provide the best outcome. The index of suspicion is directly proportional to the maternal history and risk factors. Early and accurate diagnosis of infection in the newborn is a difficult task and is often complicated by the nonspecificity of the signs associated with sepsis exhibited by the newborn. The evaluation for infection in the newborn often depends on whether EOS or late-onset sepsis (LOS) is suspected. EOS is most often defined as sepsis that presents within the first 72 hours of life; however, many infections include sepsis that occurs within the first 6 days of life. LOS is, therefore, sepsis that presents after the first week of life. Very LOS may occur up to 3 months of age, usually from group B streptococcus (GBS; Nizet & Klein, 2016).

The perfect screen for neonatal sepsis has not been determined, although some laboratory aids have been found to be very helpful in diagnosing neonatal sepsis. A CBC is often the first step in evaluating for infection. The CBC of an infected infant may reveal leukopenia (white blood cell [WBC] count $<5{,}000$ cells/mm^3), leukophilia (WBC count $>25{,}000$ cells/mm^3), or a preponderance of immature neutrophils with the immature-to-mature cell ratio (I:T) greater than 0.2. The I:T ratio is the most studied of ratios of neutrophil counts and adds a level of confidence not appreciated with Band count alone. More important may be the negative predictive value of the I:T ratio. If I:T ratios are normal, it is unlikely that the infant is septic. Keep in mind that if the CBC is obtained early in the infectious process, it may not reflect abnormalities. A follow-up CBC in 12 to 24 hours for the infant with an initially normal CBC, but who is symptomatic for sepsis, should be considered and may reflect abnormalities at that time. Use of the CRP has added another level of confidence in excluding serious infection and in evaluating the infant's response to treatment and in determining length of therapy. Serial CRPs have been found to be more reliable than a single level. In the presence of sepsis, CRP levels may be normal at the onset of symptoms but are typically elevated by 24 hours of age and remain elevated during the acute phase of infection or inflammation.

If signs of central nervous system (CNS) involvement are present, a lumbar puncture (LP) for cerebrospinal fluid (CSF) cultures is indicated, whether EOS or LOS is suspected. Since urinary tract infections are extremely uncommon during the first few days of life, a urine culture is not indicated for EOS (Shane et al., 2017). Gram stain of the CSF or urine can give an early indication of the type of microorganism responsible for the infection. Cell count and protein and glucose levels of the CSF may also indicate the presence of infection. A chest radiograph can identify the presence of pneumonia. Other tests that may be useful include latex agglutination (LA) or counter-immunoelectrophoresis (CIE) of urine or CSF or other body cavity fluids, and erythrocyte sedimentation rate (ESR). Serum procalcitonin (PCT) is a test that is gaining favor in the diagnostic evaluation of possible bacterial sepsis in older infants and adults but is not commonly used in the diagnosis of bacterial infection in the newborn. The known fluctuations seen in the newborn during the first 48 hours complicate its usefulness. Traditionally, culture-positive sepsis from blood, CSF, urine, and other body fluids is the most valid diagnostic sign.

Differential Diagnosis

The microorganisms responsible for newborn infection have changed over the past 60 years, and there are marked regional variations. Organisms responsible for EOS differ from those responsible for LOS; therefore, the antimicrobial agents of choice differ based on the timing of symptoms. Even with the implementation of prophylactic use of intrapartum antibiotics, GBS remains the leading cause of EOS followed by *Escherichia coli*. Some microorganisms, including *E. coli*, groups A and B streptococci, and *Listeria monocytogenes*, are often implicated in EOS and LOS. Other organisms, including *Staphylococcus aureus*, coagulase-negative staphylococci (CoNS), and *Pseudomonas aeruginosa*, are typically associated with LOS (Nizet & Klein, 2016).

After day 7, nosocomial microorganisms should be considered. CoNS is the most frequently identified organism in newborn infants with nosocomial infection, particularly when invasive medical devices have been used, with gram-negative organisms and fungi following. Hospitalized preterm newborns are often affected by repeated episodes of infection. Many of these episodes are termed presumed, suspected, or clinical infection because no microorganism is recovered and cultured, despite clinical evidence of infection that responds to antimicrobial agent therapy (Shane et al., 2017).

Prognosis

The introduction of broad-spectrum antimicrobial agents dramatically improved the prognosis for infection, and there has been a decline in infection-associated neonatal and infant deaths in the United States. However, infection still accounts for significant morbidity and mortality in the neonatal period. Consequences of bacterial infection include prolonged hospitalization, increased hospital costs, and increased mortality. Term infants who are promptly and adequately treated for sepsis rarely have long-term sepsis-associated health problems; however, neurologic sequelae are seen in 15% to 30% of infants with septic meningitis. Preterm infants with sepsis are more likely to experience long-term neurologic damage, especially if shock is present (Anderson-Berry et al., 2015).

Management

Management of a newborn with an infection is aimed at the traditional "ABCs": airway (including oxygen, ventilation, correction of acidosis), breathing, circulation, volume expansion, antimicrobial agents, and consideration of immune therapy. The exact management plan is based on an assessment of clinical signs, careful history, and appropriate laboratory findings with consideration of the most likely microorganisms. Treatment should begin as soon as sepsis is suspected due to the newborn's state of immunosuppression. Antimicrobial agents should be started as soon as relevant diagnostic tests have been completed (Anderson-Berry et al., 2015).

Antimicrobial Agents

The selection of antimicrobial agents is based on identification of the microorganism and the infant's response to therapy. Treatment decisions are divided into empirical (suspected sepsis) or definitive (known pathogen). The prudent use of empiric therapy is necessary in this age of increasing resistant organisms in our hospitals and communities. Infectious microorganisms are divided into two broad classes, based on Gram-stain results: gram-positive and gram-negative (Shane et al., 2017). The shape of the microorganism categorizes it as either a coccus or a rod. Generally, the gram-positive organisms respond to broad-spectrum antibiotics, such as penicillin analogues and first-generation cephalosporins (beta-lactamases), and the beta-lactamase penicillins. The gram-negative microorganisms are most often susceptible to aminoglycosides and cephalosporins. Tests must be run to determine the specific sensitivity of a microorganism to the antimicrobial agent selected to ensure that the appropriate agent is prescribed (Shane et al., 2017). In the United States and Canada, empiric therapy for EOS sepsis is generally treated with a combined approach such as intravenous (IV) ampicillin and an aminoglycoside (usually gentamicin); a third-generation cephalosporin should be considered if there is concern for meningitis (Anderson-Berry et al., 2015). This approach provides coverage for the most likely organisms, which include gram-positive organisms such as GBS and gram-negative bacteria such as *E. coli*. If LOS is suspected, antibiotic choices should be based on site of infection and those that are effective against known hospital-acquired infections such as *S. aureus, S. epidermidis,* and *Pseudomonas* species (Simonsen et al., 2014).

Generally speaking, antimicrobial choices are based on organisms known to be present in the local nursery. Gram-positive cocci generally respond to penicillin, unless the microorganism produces beta-lactamase (or penicillinase). The beta-lactamase destroys the penicillin. *Staphylococcus aureus* is a beta-lactamase–producing microorganism and is therefore not responsive to penicillin. A group of semisynthetic penicillins with added side chains are used for treatment of *S. aureus* infection. Of this group, nafcillin and oxacillin are most often used. Other similar drugs are methicillin, dicloxacillin, and cloxacillin. First-generation cephalosporins, such as cefazolin, cephalexin, and cephalothin, are also resistant to beta-lactamase. *Staphylococcus epidermidis* and *S. aureus* strains may be resistant to penicillin, semisynthetic penicillins, and cephalosporins. Methicillin-resistant *S. aureus* (MRSA) is unresponsive to the semisynthetic penicillins. In this case, vancomycin is the drug of choice (Simonsen et al., 2014). It may also be used for *S. epidermidis* and infection related to foreign bodies or invasive procedures. The emergence of resistant strains to available antimicrobial agents is an increasing problem, due to the lack of other safe and effective antimicrobial agents to treat the infection (Shane et al., 2017).

Third-generation cephalosporins are used to treat gram-negative cocci that are penicillin and methicillin resistant. Carbapenems, such as meropenem, may also be considered for extended-spectrum beta-lactamase–producing gram-negative bacilli infections. *Listeria monocytogenes*, a gram-positive rod, generally responds to ampicillin therapy. Aminoglycosides or third-generation cephalosporins are the drugs of choice for gram-negative enteric rods (Shane et al., 2017). Some gram-negative rods are classified according to their lactose fermentation ability. The lactose fermenters, *E. coli* and *Klebsiella*, are sensitive to aminoglycosides and third-generation cephalosporins. *Shigella* and *Salmonella* are nonlactose fermenters, which respond well to ampicillin and third-generation cephalosporins. *Haemophilus influenzae* is usually sensitive to ampicillin and third-generation cephalosporins, although some strains are ampicillin resistant. *Pseudomonas* requires the following combination therapy: aminoglycoside and an antipseudomonal penicillin such as azlocillin, carbenicillin, imipenem, mezlocillin, piperacillin, or ticarcillin (Simonsen et al., 2014).

Two anaerobic microorganisms, *Bacteroides fragilis* (gram-negative) and *Clostridium* (gram-positive), are sometimes the cause of newborn infections. *Bacteroides fragilis* is susceptible to metronidazole (Flagyl), clindamycin, chloramphenicol, and some of the newer beta-lactamases, such as imipenem and ampicillin with sulbactam. Clostridium is usually susceptible to penicillin. A combination of ampicillin or penicillin and gentamicin is useful for antibacterial action against *Streptococcus*, *L. monocytogenes*, and gram-negative enteric rods. This combination of antimicrobial agents has a synergistic effect (in vitro), increasing the efficacy of either drug therapy used alone. Additional therapy or selection of other agents is necessary if staphylococcal infection is suspected, if *Pseudomonas* or *Bacteroides* (most often iatrogenically acquired) is present, if there is an outbreak of resistant organisms, or if prolonged ampicillin and gentamicin therapy has been used (Simonsen et al., 2014). Antimicrobial agents must be reevaluated after completion of cultures and sensitivity testing. Tables 11.1 and 11.2 show generally recommended antimicrobial choices for infections caused by gram-positive and gram-negative microorganisms.

TABLE 11.1

GENERAL ANTIMICROBIAL SELECTION GUIDELINES FOR GRAM-POSITIVE MICROORGANISMS

Microorganism	Antimicrobial
Streptococcus	Penicillin or ampicillin
Staphylococcus aureus	Semisynthetic penicillins, such as methicillin (or methicillin-type), nafcillin, oxacillin, dicloxacillin, cephalin, cephalothin
Methicillin-resistant *Staphylococcus aureus* (MRSA)	Vancomycin
Staphylococcus epidermidis	Vancomycin
Listeria monocytogenes	Ampicillin
Clostridium difficile	Penicillin

TABLE 11.2

GENERAL ANTIMICROBIAL SELECTION GUIDELINES FOR GRAM-NEGATIVE MICROORGANISMS

Microorganism	Antimicrobial
Escherichia coli	Aminoglycosides or third-generation cephalosporins
Klebsiella	Aminoglycosides or third-generation cephalosporins
Shigella	Ampicillin and third-generation cephalosporins
Salmonella	Ampicillin and third-generation cephalosporins
Haemophilus influenzae	Ampicillin and third-generation cephalosporins; some strains are ampicillin resistant
Pseudomonas	Aminoglycoside plus an antipseudomonas penicillin
Serratia	Aminoglycoside plus an antipseudomonas penicillin
Bacteroides fragilis	Metronidazole, clindamycin, some beta-lactamases such as imipenum and ampicillin with sulbactam; and chloramphenicol

TYPES OF NEONATAL INFECTION

This section briefly describes the types of microorganisms that typically cause neonatal infection and their clinical manifestations, diagnosis, and collaborative management. The discussion includes both congenitally acquired and nosocomially acquired infections caused by bacterial, viral, fungal, and protozoal organisms.

Bacterial Infections

Group B *Streptococcus*. Group B beta-hemolytic streptococci were unknown to the perinatal scene until the early 1970s when they replaced *E. coli* as the single most common agent associated with bacterial meningitis during the first 2 months of life. Since the implementation of intrapartum antibiotic prophylaxis (IAP) for prevention of neonatal GBS disease, rates of EOS with GBS have declined; however, GBS sepsis continues to be the most common pathogen in term infants.

Epidemiology. The number of newborn deaths associated with either early-onset or late-onset GBS continues to be high, particularly in high-risk urban centers. Potential for permanent neurologic sequelae for infant survivors of meningeal infections is approximately 15%. The mortality rate of infected newborns varies according to time of onset. Early-onset infection (within the first week of life) has a mortality rate of 8%, which is decreased from 50% in the 1970s; late-onset (after first week of life) mortality is approximately 3% (Nizet & Klein, 2016). Although the incidence of GBS EOS has declined, universal screening and intrapartum antibiotic prophylaxis (IAP) has not resulted in a decline in the incidence or morbidity of LOS. More research is needed related to disparity and the burden of prenatal GBS (Kimberlin, Long, Brady, & Jackson, 2018; Verani, McGee, & Schrag, 2010).

GBS is a gram-positive diplococcus with an ultrastructure similar to that of other gram-positive cocci. It was classified as hemolytic because of its double zone of hemolysis surrounding colonies on blood agar plates. Culture of body fluids, such as blood, urine, CSF, and other secretions, is the most common method of identifying group B streptococci. More rapid techniques, DNA probe assays, LA assays, and nucleic acid amplification assays, such as polymerase chain reaction (PCR), enable a presumptive diagnosis before cultures are returned. Rapid identification of the GBS organism is important in treating colonized pregnant women and in the early diagnosis and treatment of infection in the sick, unstable septic infant. To accurately predict maternal colonization with group B streptococci, both vaginal and rectal areas should be cultured on more than one occasion (Kimberlin et al., 2018; Veranit et al., 2010).

Clinical Manifestations. GBS has been identified as a relatively common cause of mid-gestational fetal loss in women who experience vaginal hemorrhage, PROM, fetal membrane infection, and spontaneous abortion. The rate of stillbirth is reported to be as high as 61% in association with these bacteria. Early-onset neonatal infections with GBS can be asymptomatic or can manifest with severe symptoms of respiratory distress and shock, which can rapidly progress to death (Nizet & Klein, 2016).

Early-Onset Group B *Streptococcus*. Early-onset GBS infection usually appears within the first 24 hours of life and is most common in premature infants. Congenital pneumonia is a more common presentation sign in infants who weigh 1,000 g or less. The most common presentations are pneumonia and meningitis. Signs of respiratory distress, apnea, grunting, tachypnea, and cyanosis are common. Hypotension is found in 25% of newborns with GBS infection; these infants are at risk for cardiopulmonary collapse. Nonspecific signs of infection include lethargy, poor feeding,

temperature instability, abdominal distention, pallor, tachycardia, and jaundice. Experienced nurses may observe that the neonate "just doesn't look right," which is sometimes a critical point for early detection and implementation of therapy. Overwhelming GBS septicemia is often compounded by meningitis. LP and examination of the CSF are the only way to exclude meningeal involvement and therefore represent an important part of the workup. Seizures may occur in infants with GBS meningitis. Low birth weight (LBW) infants have been identified as particularly vulnerable, but a study in Texas revealed a high incidence of infection in term newborns. These infants had no risk factors for infection; therefore, there was a delay in identification and treatment. The mortality rate in these term newborns was 14% (Nizet & Klein, 2016).

Late-Onset GBS Infection. Late-onset infection with GBS usually occurs in term newborns 7 days to 12 weeks of age. The fatality rate is less than that with early-onset infection, but meningitis may lead to permanent neurologic damage, varying in severity from mild handicaps to severe impairment. Complications include global or profound intellectual disability, spastic quadriplegia, cortical blindness, deafness, uncontrolled seizures, hydrocephalus, and diabetes insipidus. Thus, early treatment is an important part of the prevention of long-term serious sequelae. An infant with a positive blood culture can often be asymptomatic initially. The diagnosis of GBS infection is complicated because signs and symptoms of neonatal infection are not specific and symptoms may represent other conditions of the neonate. For example, apnea may be a symptom of CNS immaturity in the preterm neonate, but it is also associated with infection. The caregiver must have a high index of suspicion for infection in all conditions involving the neonate. Infection should be considered in the differential diagnosis of most newborn illnesses. Screening tests, such as CBC with differential, are often used to identify the need for further evaluation for infection. Abnormal results indicate the necessity for definitive testing and implementation of antimicrobial therapy.

Treatment. Regional and hospital differences in infectious agents must be considered in the selection of antimicrobial therapy. Before culture results are returned, administration of a broad-spectrum penicillin and an aminoglycoside provides coverage for the most prevalent microorganisms. Generally, ampicillin and gentamicin are selected until culture results and sensitivities are available. Although most strains of GBS are resistant to aminoglycosides, there is a synergistic effect observed when gentamicin and ampicillin are used in combination until these results are known. GBS is generally very sensitive to penicillin G, and, in many institutions, penicillin G is substituted for ampicillin once the diagnosis is made. It is acceptable practice to discontinue gentamicin when cultures confirm GBS infection. Therapy is maintained for 7 to 10 days for uncomplicated bacteremia or pneumonia and 14 to 21 days for meningitis (Edwards, Nizet, & Baker, 2016; Simonsen et al., 2014). The LP may be repeated midway or at the end of therapy to ensure that there are no microorganisms remaining in the CSF. Fluid management, volume expansion, and appropriate antimicrobial therapy are the key components of nursing care. Infants with GBS infection are often very labile and do not tolerate frequent interventions. Minimal handling is sometimes required for their care.

Prevention. The most potentially lasting method for prevention of early- and late-onset infections, as well as maternal morbidity associated with GBS, appears to be active immunization of all women of childbearing age, either before pregnancy or late in pregnancy (at ~7 months gestation). Passive transmission of antibodies to the newborn occurs via the placenta; however, women often deliver infants prematurely, before the successful transmission of appropriate protective antibodies. Because 65% to 85% of all infants with GBS disease are born at term, vaccines given to women early in the third trimester could prevent up to 95% of these infections. The cost of developing a suitable vaccine would probably be less than the cost of the care required by the critically ill newborn and the chronically ill, debilitated, severely handicapped newborn. To date, there are no licensed maternal vaccines for neonatal GBS prevention, although much research has been done and development is progressing (Edwards et al., 2016).

Staphylococcus. *Staphylococcus* is another gram-positive bacteria. From the 1950s to the 1970s, coagulase-positive *S. aureus* was the main organism identified as a pathogen in hospitals. In the 1980s, coagulase-negative organisms, in particular *S. epidermidis*, were discovered to be equally important.

Epidemiology. These organisms have caused many serious and even fatal infections in newborns. Critically ill and preterm newborns are already immunocompromised and therefore are especially vulnerable to infections. Open skin lesions, surgical incisions, or puncture wounds caused by diagnostic tests or procedures are conducive to bacterial growth, especially *S. aureus* or *S. epidermidis*. Nosocomial infections may also be transmitted to the neonate through contaminated articles or from the hands of healthcare providers. Overgrowth of *S. epidermidis* may occur in nurseries where an attempt has been made to reduce colonization of *S. aureus*. Development of resistant organisms is a risk for critically ill or preterm infants who require extensive invasive treatments. CoNS or MRSA have a potential for causing a wide variety of significant clinical syndromes including those with high mortality. Staphylococci release endotoxins that have systemic effects, including alterations in the skin's protective layer. Scalded skin syndrome is one of the most common examples of this effect (Bradley & Nizet, 2016).

Treatment. Management and supportive therapy for staphylococcal infection are initially the same as for infection with group B streptococci. Antimicrobial therapy begins with ampicillin and gentamicin. Once definitive cultures and sensitivities are available and if the organism is ampicillin resistant, the drug of choice is one of the synthetic penicillins: oxacillin, methicillin, cloxacillin, dicloxacillin, or nafcillin. If the organism is methicillin resistant, the best available drug is vancomycin. It is essential that the choice of antimicrobial agent be carefully made and reconsidered when culture results are available.

Escherichia coli. *E. coli* is second to GBS as the most common cause of EOS and is the most common cause of gram-negative infection in the newborn.

Epidemiology. *E. coli* is associated with preterm delivery, LBW, prolonged ROM, intrapartum fever, and maternal chorioamnionitis (Mendoza-Palomar et al., 2017). As with other maternal organisms that are associated with the GI tract, coliform organisms are common in the maternal birth canal, causing a high incidence of colonization in the lower GI or respiratory tract of newborns during labor or at delivery (Nizet & Klein, 2016).

Treatment. Uncomplicated bacteremia due to susceptible organisms should be treated for 14 days following the first negative culture while meningitis should be treated for a minimum of 21 days. Although there appears to be increasing resistance to ampicillin and gentamicin in the United States, this combination remains the best choice for empiric therapy (Simonsen et al., 2014). Use of third-generation cephalosporins for empiric therapy is not recommended due to increasing resistance unless gram-negative meningitis is highly suspected (Leonard & Dobbs, 2015). **Emergency Alert: Due to increasing ampicillin resistance patterns, it is important to follow blood culture sensitivities when treating organisms with ampicillin.**

Listeria monocytogenes

Epidemiology. *L. monocytogenes*, a gram-positive rod, has been recognized as a cause of perinatal complications since the early 1900s. In the United States during 2009 to 2011, 1,651 cases were reported to surveillance systems with a case-fatality rate of 21%. Those at greatest risk are older adults, pregnant women, and immunocompromised individuals. *Listeria* is found in birds and mammals, including domestic and farm animals, and in unpasteurized milk, soil, and fecal material (Kollmann, Mailman, & Bortolussi, 2016; Leonard & Dobbs, 2015).

Clinical Manifestations. A mother infected with *Listeria* commonly has flulike symptoms, including malaise, fever, chills, diarrhea, and back pain. It is also possible to contract the infection and remain asymptomatic or have only minor symptoms. If contracted between 17 and 28 weeks' gestation, *Listeria* can cause fetal death or premature birth of an acutely ill newborn who may develop EOS or LOS or meningitis. However, early maternal treatment with IV ampicillin and gentamicin has been associated with a normal newborn outcome. Infection late in pregnancy may cause the infant to be born with a congenital infection, usually pneumonia. Mortality rates are high but are usually related to the degree of prematurity. Late-onset listeriosis, which can occur up to 4 weeks after delivery, can easily result in meningitis. A term newborn with listeriosis has less chance of dying but often suffers complications of hydrocephalus and intellectual disability. However, in either preterm or term neonates in whom meningitis develops, there is a 70% mortality rate if treatment is delayed. Newborns infected with *Listeria* may be meconium-stained (or have brown-colored amniotic fluid), exhibit apnea and flaccidity, have a papular erythematous skin rash and hepatosplenomegaly, and be poor feeders. Preterm birth associated with the appearance of meconium staining of amniotic fluid should always be considered suspicious for listeriosis (Kimberlin et al., 2018; Kollmann et al., 2016).

Treatment. Intrapartum administration of antibiotics may decrease fetal morbidity and mortality rates. Ampicillin in combination with an aminoglycoside is the most common treatment. Investigators have shown that newborn survival rates are significantly different if the mother as well as the infant receives treatment (71% vs. 29%; Kollmann et al., 2016). Treatment for bacteremia is typically 14 days, whereas meningitis is treated for 21 days. It is suggested to perform diagnostic imaging of the brain near the end of the anticipated treatment course to evaluate if prolonged therapy is needed for parenchymal involvement of the brain. Careful handwashing is a very important aspect of caring for the infant infected with *Listeria*. Institutional policy may require that the infant be isolated for the first 24 hours of life, until the antibiotics are on board. The mother's urine, stool, and lochia should be cultured, and if positive, she should be given ampicillin. Listeriosis often presents suddenly in the last trimester of pregnancy, precipitating an unexpected preterm delivery. Extensive emotional support may be necessary for the mother and family. In the United States, listeriosis is a nationally reportable disease for state or local health departments (Kimberlin et al., 2018).

Neonatal Meningitis

Epidemiology. Meningitis is commonly associated with newborn infection. The single most important factor in the enhanced risk for sepsis or meningitis in the newborn is LBW (Nizet & Klein, 2016). Mortality rates have decreased over the past decades but remain estimated at 10% to 20%. Meningitis can be associated with both early- and late-onset infection but is more common as a complication of late-onset infection (Leonard & Dobbs, 2015). In most cases, meningitis results from bacteremia. Thus, an inoculation of organisms may pass the blood–brain barrier and infect the CSF.

Although the overall incidence of neonatal bacterial meningitis in developed countries is less than 1%, the incidence is much higher in preterm and VLBW infants. Male infants are more vulnerable to infection and, consequently, meningitis. Female infants have lower rates of respiratory distress syndrome and lower rates of most congenital infections. Geography and socioeconomic factors are influential in patterns of neonatal disease. These differences probably reflect populations served, including unique cultural activities and sexual practices, as well as local customs. It probably also reflects different treatment patterns in local nurseries and variations of antimicrobial selections (Gupta, Roa, Al-Mufti, & Roychowdhury, 2018).

Clinical Manifestations and Diagnosis. Initially, the infant with meningitis presents with signs and symptoms of generalized infection. In addition, the meningeal irritation results in increased irritability, alterations in consciousness, lethargy, tremors or twitching, seizure activity, and diminished muscle tone. Focal signs include hemiparesis, horizontal deviation of the eyes, and some cranial nerve involvement. Bulging fontanelles may or may not be a presenting finding due to the flexibility of the cranial sutures (Nizet & Klein, 2016). The most common organisms responsible for bacterial meningitis are GBS (50%), *E. coli* (20%), and *L. monocytogenes* (5%–10%). Herpes simplex virus (HSV) is a major cause of neonatal viral meningitis and carries a 50% risk for neurologic sequela (Gupta et al., 2018). Cytologic tests on the CSF can identify the presence of an inflammatory response. A Gram stain of the CSF fluid should be prepared and other appropriate cultures obtained. High CSF protein and low glucose levels are also indicators of meningitis, although parameters may overlap between those with and without meningitis. As with all procedures in the neonate, the LP presents risks, which must be weighed against the benefit of having a CSF culture. Often the preterm infant may be considered so critically unstable that the LP is deferred (Leonard & Dobbs, 2015).

Treatment. The selection of antimicrobial therapy for meningitis is based on the causative microorganism. Supportive therapy is necessary for the newborn with meningitis. Acute observation and monitoring of vital signs and activity level are crucial. Infants who become critically ill with meningitis may deteriorate quickly and need rapid, acute interventions. Infants often require long-term antibiotic therapy, and often, venous access is a problem. Placement of a percutaneous line for parenteral nutrition may be necessary. Families need educational and emotional support during long-term hospitalizations, particularly if complications develop. Because signs and symptoms of neonatal infection are nonspecific and are often the same, with or without meningitis, it is imperative to begin empiric therapy once suspicion is established. Empiric therapy for sepsis of unknown etiology remains initiation of broad-spectrum antibiotics, generally ampicillin and gentamicin. When meningitis is highly suspected, cefotaxime is also used. It is important to realize that cephalosporin-resistant strains of many gram-negative bacteria are emerging. Resistance of *E. coli* and *Klebsiella* species to ampicillin, gentamicin, and the cephalosporins continues to make treatment choices more difficult (Gupta et al., 2018).

Prevention. Preventive measures are in place for the most common causes of neonatal meningitis. GBS prophylaxis and IAP for mothers who tested positive for GBS or have certain risk factors has shown a steady decrease in EOS GBS sepsis and meningitis. Control measures for *Listeria* and *E. coli* include avoidance of certain foods by pregnant women as well as those who may become pregnant. Foods that are known to be at risk for being contaminated with listeria include soft cheeses made with unpasteurized milk, uncanned smoked seafood, and unpasteurized milk. The

food industry must be strict with the handling of foods in order to prevent the growth of *Listeria* and *E. coli*. The most likely foods for contamination are raw sprouts, melons, and meats such as hot dogs, deli meats, and cold cuts (Gupta et al., 2018).

Prognosis. Mortality from neonatal meningitis has decreased dramatically with higher rates among preterm infants; substantial neurologic morbidity continues to be seen among survivors. Complications of neonatal meningitis include mental and motor problems, seizure disorders, hydrocephalus, hearing loss, blindness, and abnormal speech patterns. It is estimated that 21% to 38% will have mild deficits and 24% to 29% will have severe neurologic sequelae (Leonard & Dobbs, 2015).

Congenital TORCH Infections

The microorganisms most often responsible for congenitally acquired infections have been grouped together as the TORCH infections. These include toxoplasmosis, others, rubella, cytomegalovirus (CMV), and herpes. The "others" category includes various microorganisms that have been responsible for congenital infections. However, the list of microorganisms implicated in congenital infections has grown, so the acronym is no longer inclusive. A more appropriate acronym, ToRCHES CLAP, is suggested by Maldonado et al. (2016). This new acronym includes: **To**, *Toxoplasma gondii*; **R**, rubella; **C**, CMV; **H**, HSV; **E**, enteroviruses; **S**, syphilis (*Treponema pallidum*); **C**, chickenpox (varicella-zoster virus [VZV]); **L**, Lyme disease (*Borrelia burgdorferi*); **A**, acquired immunodeficiency syndrome (AIDS/HIV); and **P**, Parvovirus B19 (Maldonado et al., 2016).

Toxoplasmosis. Initially thought to be an animal disease, the clinical importance of the parasite *T. gondii* in humans gained importance throughout the 1900s. Toxoplasma is a pathogen that is ever present in nature worldwide (Peyron, Wallon, Kieffer, & Garweg, 2016). The life cycle of Toxoplasma is complicated. The predominant host of this organism is the ordinary house cat that has ingested contaminated meat or fomites excreted by other infected cats; however, other animals, such as farm animals (cows, pigs, and sheep), can become infected if they ingest food or water containing cat feces with oocytes present (Kaufman & Manzoni, 2015). The oocyte form of the parasite persists in soil contaminated by cat feces.

Epidemiology. Congenital toxoplasmosis is transmitted from the mother to the fetus after ingestion of undercooked meat or food or from fomites in cat feces. Risk of infection by the pregnant woman is related to certain activities such as changing litter boxes, playing with children in sandboxes, and gardening in soil used by cats. Congenital toxoplasmosis is almost exclusively the result of primary maternal infection. Transmission rate during pregnancy is directly related to the gestational age of the fetus when maternal infection occurs (lowest during the first trimester increasing up to as high as 60% transmission during the third trimester). On the other hand, there is an inverse relationship between timing of infection and fetal damage (first trimester infection will have more devastating fetal effects compared with third trimester acquisition; McAuley, 2014). The risk of infection when the mother was infected prior to pregnancy is extremely low, except in the immunocompromised woman (McLeod, VanTubbergen, & Boyer, 2016). After infection in the mother, the microorganisms invade and multiply within the placenta and eventually enter the fetal circulation. The greatest risk is when a nonimmune pregnant woman is exposed to *T. gondii* during fetal organogenesis (weeks 4–8 of gestation), when the risk for congenital anomalies is high. In the United States, approximately 20% to 70% of the population has been exposed to this protozoan. There is wide variability in the prevalence of seropositive women of childbearing age among countries, geographic regions of the same country, and ethnic origin; different cultural practices regarding food are probably the major cause of this difference. Since meat is the main vector for transmission, areas where there is less *T. gondii* present in meat because of improved methods for processing or cooking meat have lower prevalence rates (Peyron et al., 2016).

Clinical Manifestations and Diagnosis. Acute toxoplasmosis in a pregnant woman often goes undetected and undiagnosed because the signs and symptoms are not severe. Clinical questioning after the identification of an infected newborn or infant often leads to reflection and memories of a period of enlarged lymph nodes and fatigue without fever. Women sometimes report a mononucleosis-like or flulike syndrome that may have a febrile course, with malaise, headache, fatigue, sore throat, and sore muscles. These symptoms may persist for several months. A newborn with congenital toxoplasmosis can present with the classic triad of hydrocephalus, chorioretinitis, and intracranial calcifications, especially in infants of mothers who were not treated during pregnancy. There are a wide variety of clinical signs in the scope of the disease and many of these closely mimic congenital CMV. The newborn can appear normal at birth, or exhibit severe erythroblastosis, hydrops fetalis, and other clinical signs. Neurologic signs similar to encephalitis (e.g., convulsions, bulging fontanelles, nystagmus, and increased head circumference) may be the only significant presentation of this clinical problem. If the newborn receives treatment, signs may disappear, allowing normal cerebral growth and development, if there was no permanent neurologic damage (McLeod et al., 2016; Peyron et al., 2016).

Mild cases of the disease may not be recognized in the newborn period. Signs of delayed onset of disease in premature newborns include severe CNS or eye lesions appearing at 3 months of age. In term newborns, delayed disease may occur in the first 2 months of life and is usually mild. Clinical signs include generalized infection, enlarged liver and spleen, late-onset jaundice, enlarged lymph nodes, or late-onset CNS problems, including hydrocephalus and chorioretinitis. Infants with congenital toxoplasmosis may have new lesions appearing until age 5 years (Peyron et al., 2016). When congenital toxoplasmosis is suspected, neonatal peripheral blood for Toxoplasma IgG and IgM immunosorbent agglutination assay should be sent to a reference laboratory. Serum transaminase tests and a CBC with differential should also be obtained (Kimberlin et al., 2018).

Treatment. Treatment for congenital toxoplasmosis is pyrimethamine plus sulfonamides. The suggested dose is 2 mg/kg/day orally for 2 days followed by 1 mg/kg/day for 2 or 6 months, then 1 mg/kg/day every Monday, Wednesday, and Friday for a 12-month total duration of treatment. Sulfadiazine is given in doses of 100 mg/kg/day in two divided oral doses. Leucovorin 10 mg is given three times weekly during and for 1 week after pyrimethamine therapy to minimize toxicity. Close monitoring is necessary during therapy due to the possibility of toxicity. Corticosteroids are given in the form of prednisone at 1 mg/kg/day in two divided doses until there is resolution of elevated protein in CSF or active chorioretinitis. As expected, it is evident that the outcome for infants with congenital toxoplasmosis is much better when treatment is given than for those without treatment (Kimberlin et al., 2018; Peyron et al., 2016). Nursing management is supportive and dependent on the severity of the infection. Neurologic impairment at birth can be significant, requiring ventilation and seizure control.

Prevention. The best and most effective treatments are prevention and early recognition. The cost-effectiveness of pregnancy serology screening depends on the costs of the tests and the estimated cost of treating the infection, if identified early. At present, in the United

States, screening is done erratically and there are no particular screening standards. Counseling education for the prevention of toxoplasmosis in seronegative women should focus on avoidance of raw meat and use of gloves during feline litter box handling and during gardening in what may be contaminated soil. Toxoplasmosis cannot be contracted by merely handling or being around a cat, so it is not necessary for the family cat to be banished. It is imperative for pregnant women to inform their healthcare provider if they experience any signs that could be attributed to *T. gondii* infection. Transmission of toxoplasmosis in humans occurs only from mother to child; therefore, the risk to healthcare personnel is negligible. There is a theoretical risk from contaminated urine, however (Kimberlin et al., 2018).

Rubella. Rubella (German measles) is usually a mild disease of infants and children involving a variable rash and fever; it is more severe and associated with more complications in adults. The clinical significance for infants is transplacental infection leading to congenital rubella syndrome (CRS). CRS is commonly recognized as a constellation of defects seen in a newborn with congenital rubella infection. These include a combination of ophthalmological defects, congenital heart defects, and hearing loss, with or without CNS complications (Mason, 2016; Reef & Plotkin, 2016).

Epidemiology. The spread of endemic rubella, and consequently CRS, has been eliminated in the United States. The only reported cases of rubella appear to have been imported from countries where the disease remains endemic. Prior to the initiation of the rubella vaccine in 1996, the incidence of rubella was 78% higher and the incidence of CRS was 69% higher than after 1996. A two-dose regime was implemented following a resurgence of both rubella and CRS between 1989 and 1991. This new schedule has been successful in controlling the disease in the United States but elimination of rubella has not been achieved nationally. Due to this, high levels of immunity must be maintained in the United States (Mason, 2016; Reef & Plotkin, 2016).

Most cases of CRS occur after a primary maternal infection with subsequent viremia and intrauterine transmission. Effects on the fetus are related to the timing of the infection during the pregnancy. First trimester infection carries the highest morbidity for the fetus. There may be fetal death, stillbirth, or CRS. Some fetuses are unaffected and not all affected fetuses develop CRS. The placenta is an effective barrier during the 12th to 28th weeks; however, the fetus is very vulnerable in the first and third trimesters (Baley & Gonzalez, 2015).

Clinical Manifestations and Diagnosis. A presumptive diagnosis of CRS should be high on the differential diagnosis list for any infant born to a mother with documented or suspected rubella during her pregnancy. The diagnosis should also be considered for any infant with presenting signs known to be associated with CRS. The abnormalities most commonly associated with CRS are auditory (e.g., sensorineural deafness), ophthalmic (e.g., cataracts, microphthalmia, glaucoma, chorioretinitis), cardiac (e.g., patent ductus arteriosus, peripheral pulmonary artery stenosis, atrial or ventricular septal defects), and neurologic (e.g., microcephaly, meningoencephalitis, intellectual disability). In addition, infants with CRS frequently exhibit both intrauterine and postnatal growth restriction. Other conditions sometimes observed among babies who have CRS include radiolucent bone defects, hepatosplenomegaly, thrombocytopenia, and purpuric skin lesions. Newborns who are moderately or severely affected by CRS are readily recognizable at birth, but mild CRS (e.g., slight cardiac involvement or deafness) may be detected months or years after birth, or not at all (Baley & Gonzalez, 2015; Mason, 2016; Reef & Plotkin, 2016).

The possibility of subclinical infection with rubella highlights the need for laboratory confirmation. Attempting to isolate rubella virus in tissue culture is very valuable in the diagnosis of CRS. The virus is readily obtainable from the posterior pharynx with less reliability from specimens obtained from the conjunctivae, spinal fluid, or urine. Specimens should be obtained as soon as CRS is suspected as viral shedding decreases during infancy. The detection of rubella antibody confirms the presence of the infection. Cord serum is a reliable source of assay for the presence of rubella-specific IgM because IgM is fetally derived. Rubella-specific IgG persists for life and can be detected by enzyme immunoassay (EIA). Demonstration of rubella-specific IgM in fetal blood obtained by cordocentesis has been used to establish diagnosis in utero. Chorionic villus sampling has also demonstrated recovery of the virus during the first trimester (Baley & Gonzalez, 2015; Reef & Plotkin, 2016).

Treatment. Unfortunately, there are no specific treatment modalities available for either rubella or CRS. Treatment is supportive and related to the associated complications. CRS is not a static disease and the primary physician must take efforts to define the extent of the associated problems and coordinate efforts to maintain a broad, multidisciplinary approach to the infant's care. Ongoing care of an infant with CRS involves follow-up and evaluation by pediatricians, cardiologists, audiologists, ophthalmologists, and neurologists. Hearing screens are particularly important, as intervention is known to improve outcome in hearing (Mason, 2016).

Prevention. The primary goal in the United States is to eliminate rubella with vaccination as active immunization is the only practical means to prevent CRS. Control techniques include isolation of those infected with rubella. Patients are considered infectious from the seventh day before onset of symptoms to the fifth to seventh day after onset of rash. Children with CRS are considered infectious for the first year unless repeated pharyngeal or urine cultures are negative (Reef & Plotkin, 2016). Reports of rubella epidemics in Japan, Poland, and Romania, with cases of CRS, are mostly attributed to cost, lack of public awareness, and public health commitments (Lambert, Strebel, Orenstein, Icenogle, & Poland, 2015). These recent epidemics highlight the importance of possible resurgence as a result of misunderstandings and parental refusal for vaccinations during childhood. There is much speculation that the incidence of many preventable infections will increase as a result of parental refusal of childhood immunizations. It will be prudent to follow any trends.

Cytomegalovirus. CMV, a member of the herpes family, is the most common congenital viral infection in developed countries. CMV is a DNA virus covered with a glycoprotein coat that closely resembles the herpes virus and VZV.

Epidemiology. CMV infection is endemic and, although it has been identified in the great apes, it is believed that humans are the only host. By adulthood, most people have been exposed to CMV, and antibodies have developed to it. CMV infection is more prevalent in lower socioeconomic groups and is especially common in developing countries. In the United States, CMV prevalence is thought to be 58.9% with racial differences noted. African American and Hispanic populations show higher seroprevalence than do white populations. The virus is usually transmitted from person to person through body fluids and secretions. Blood, urine, breast milk, cervical mucus, semen, and saliva harbor CMV. The virus can cause an infectious mononucleosis-like syndrome, with general malaise, liver complications, fever, and general fatigue (Baley & Gonzalez, 2015; Britt, 2016). Transplacental transmission is directly related to advancing gestational age with up to 75% risk during the third trimester. Congenital infection is associated with more severe sequelae when acquired during the first half of pregnancy (Kimberlin et al.,

2018). Although infection of the fetus can occur at any time during pregnancy, the risk of malformations and developmental delays is most common during the period of organogenesis (Baley & Gonzalez, 2015). Perinatal transmission can occur within 2 to 3 days of infection by transplacental crossing of the organism. The fetus can also contract the virus intrapartally from infected maternal cervical secretions while descending through the birth canal. CMV can also be transmitted through infected breast milk. CMV infection may occur at any stage of gestation and is not always the result of a primary maternal infection. Congenital CMV occurs in approximately 0.15% to 2% of all newborn infants (Britt, 2016).

Clinical Manifestations and Diagnosis. Congenital CMV is divided into two categories, symptomatic congenital CMV and asymptomatic congenital CMV. The majority of infants identified with congenital CMV will not present with symptoms at birth (asymptomatic). Infants who do not present with symptoms at birth generally have a better prognosis; however, approximately 10% will develop sensorineural hearing loss (SNHL). Congenital CMV infection is the leading nongenetic cause of SNHL in the United States, occurring in up to 50% of children with symptomatic illness at birth (Kimberlin et al., 2018). These infants require close follow-up for neurologic and motor defects as well as chorioretinitis. Symptomatic disease is most often accompanied by intrauterine growth restriction, microcephaly, periventricular calcifications, SNHL, chorioretinitis, congenital cataracts, profound intellectual disability, hepatosplenomegaly, and jaundice (Boppana, Ross, & Fowler, 2013; Britt, 2016; Swanson & Schleiss, 2013).

Suspicious clinical findings or obstetric history warrant further investigation for CMV infection. Diagnosis in the neonate can be confirmed by viral detection in bodily fluids or PCR, culture, or antigen testing. Preferred specimens include urine and saliva due to the high viral load found in these specimens. After the first 3 weeks of life, congenital versus postnatally acquired disease cannot be distinguished. IgG and IgM antibody titers cannot reliably be used in diagnosis. Elevated IgM in the first 2 weeks of life reflects fetal antibody response to CMV; however, after 2 weeks, elevated titers may be related to postnatal acquisition of the virus. Elevated neonatal IgG titers may reflect seropositive status of mothers with the IgG antibodies becoming undetectable between 4 and 9 months in the uninfected infant; in the infected infant, these antibodies persist for a much longer interval (Britt, 2016; Kimberlin et al., 2018; Swanson & Schleiss, 2013).

Treatment. Newborns infected with CMV display a wide range of signs and symptoms. General supportive therapy is based on the presence of these clinical manifestations. Treatment with antivirals offers the best outcome for infants with symptomatic CMV. The most beneficial treatment is ganciclovir, whose structure is similar to that of acyclovir (ACV). This drug has been found to be generally safe and well tolerated by newborns. IV therapy is typically started until a PCR response is noted; therapy can then be completed by oral route with valganciclovir. It is important to involve an infectious disease specialist, who can follow the infant after discharge and recommend length of needed therapy (Britt, 2016; Kimberlin et al., 2018; Swanson & Schleiss, 2013). IV immunoglobulin therapy provides passive immunity to at-risk infants but not to those already infected. Two live attenuated vaccines for CMV have been developed and tested on renal transplant patients. Theoretically, these vaccines would be useful preconceptionally or perinatally to prevent vertical transmission; however, only limited research has been done with this population. Chemotherapy offers the most promise for treatment of neonatal CMV infection; however, clinically, it has not been shown to be effective in improving long-term outcome (Britt, 2016; Swanson & Scheiss, 2013).

Prevention. CMV is a common and often undiagnosed infection. Prevention of spread of the virus is virtually impossible due to the lack of symptoms in most hosts. Careful surveillance of childbearing women will assist in recognizing the risk of infection in the newborn. Hospital workers who are of childbearing age are often concerned about their risk for contracting CMV from their virus-shedding patients. Generally, this risk is dependent on the prevalence of CMV secretion, the susceptibility of the worker, and the degree of exposure. Since implementation of universal precautions, the risk of nosocomial transmission of the virus has been very low and is considered lower than the risk of acquiring the infection in the community (Britt, 2016). Transmission of CMV via infected blood products has been significantly decreased through the use of CMV-negative donors or irradiation of blood products. Premature and LBW infants are especially vulnerable to the infusion of this virus in blood products. The best method of prevention is the institution of universal precautions, including good handwashing techniques.

Herpes Simplex Virus.

HSV Types 1 and 2 are members of a family of large DNA viruses. Common sites of infection include the skin, oral mucosa, eyes, and genital tract. Although these two types are capable of causing primary infection at any site, Type 1 is more likely to cause recurrence at oral mucosal sites and Type 2 has a greater propensity for recurrence at genital sites (Stanberry, 2006).

Epidemiology. Neonatal infection can result from either type with a worldwide estimate of 75% of cases caused by HSV Type 2 and 25% of cases of Type 1 (Allen & Robinson, 2014). HSV possesses the quality of "latency," whereby the virus can persist in a latent state for a period of time and then be reactivated by certain stimuli. A strand of the viral DNA persists in an infected individual for a lifetime; thus, the virus maintains a "foothold" in its host. Clinical experiences demonstrate that, after primary HSV infection, at the site of the infection (perhaps an oral or genital site) the microorganism invades the sensory nerve endings and remains there (Kimberlin & Gutierrez, 2016). Primary infections appear to be more severe as the host is seronegative. Potential stimuli for HSV reactivation include periods of stress, emotional trauma, and prolonged exposure to the sun (Baley & Gonzalez, 2015). Maintenance of the latency state and recurrence of the virus are topics of intense current research. There are many unanswered questions about what triggers latency and about the cofactors for reactivation of the virus.

Greater than 90% of neonatal HSV infection is the result of maternal–fetal transmission, with up to two-thirds of cases occurring in women with an asymptomatic primary infection. Transmission of the infection to the fetus can be caused by passage through infected genital secretions in the intrapartum period or by ascending infection from the vaginal vault via ruptured (or not) membranes. Many women can be asymptomatic and still be shedding HSV. Recurrent infections are the most common problem in pregnancy. The risk is greater with primary or non-primary first infection than with exposure from a recurrent infection. Although primary infection is less common, it causes the most severe neonatal disease, most likely including CNS problems, disseminated disease into other organ systems, and probable death. During a primary maternal genital infection there is a higher viral load, prolonged viral shedding, and little or no passive maternal antibodies resulting in higher incidence of fetal or neonatal infection. The incidence of intrapartum transmission with a primary infection or non-primary first infection is approximately 30% to 50%. Many neonatal complications such as prematurity, intrauterine restriction, and respiratory distress syndrome can potentiate the neonate's illness, limiting the ability

to fight off HSV. There is a broad range of severity of neonatal infection, from severe to benign and asymptomatic. HSV is the most reported cause of fatal encephalitis in both children and adults (Stanberry, 2006).

Intrapartal transmission is more likely to occur in the presence of ruptured membranes. Other risk factors include intrauterine fetal monitoring, fetal scalp sampling, and other instrumentation such as forceps or vacuum-assisted delivery. It is recommended that women infected with HSV not be monitored by these methods (Baley & Gonzalez, 2015). Transmission from mother to infant from an infected breast lesion has been reported. Transmission has also been documented from oral lesions.

Clinical Manifestations and Diagnosis. Acquisition of HSV in utero can result in spontaneous abortion, preterm birth, or a normal baby. Clinical manifestations of the disease are broad and are related to the initial site of infection or category. The clinical presentation of the congenital acquisition of the infection includes skin vesicles or scarring, hypopigmentation, chorioretinitis, microcephaly, and hydranencephaly. There are three categories of neonatal HSV disease. These categories may occur in isolation or there can be overlap of presentation. The first category, the most common, includes patients with localized infections of the skin, eyes, or mouth (SEM disease). The typical skin finding is a cluster of discrete vesicles on an erythematous base. The second category includes patients with encephalitis (CNS disease). In this group, neurologic sequelae occur in approximately 50% and mortality is high in untreated HSV encephalitis. Approximately one-third of these patients do not have skin vesicles, and they are identified by history alone. CSF is positive for the virus in 25% to 40% of these cases. Presence of cells and increased protein are very common in the CSF of patients with encephalitis. The third category of neonatal patients includes those with disseminated disease characterized by irritability, seizures, respiratory distress, jaundice, DIC, shock, and other symptoms of viral and bacterial infection. All major neonatal organs may be involved. Liver and the adrenals are the most common reservoirs for the virus. The CNS is involved in 70% to 90% of affected neonates. In greater than 40% of the newborns with disseminated disease, skin vesicles do not develop or develop late, making identification of positive infants more difficult. The mortality rate for untreated disseminated disease is greater than 80%, making early and accurate diagnosis a priority in the ill newborn (Baley & Gonzalez, 2015; Kimberlin & Gutierrez, 2016). **Emergency Alert: HSV infection should be considered in any clinically ill, septic appearing neonate with negative bacterial cultures. Fever is also highly suggestive, especially within the first 3 weeks of life.**

Expert consultation is important in the early stages of identification and evaluation. Laboratory tests are available to differentiate HSV infection from other bacterial and viral infections but must be interpreted with consideration of the clinical context (Allen & Robinson, 2014). Routine surface cultures of the newborn from oral mucous membranes, rectum, nasopharynx, and conjunctivae should be delayed to 24 to 48 hours after birth to differentiate viral replication from transient colonization of the newborn at birth. Earlier testing from these sites may confound the results (Baley & Gonzalez, 2015; Kimberlin & Gutierrez, 2016). The clinical diagnosis of neonatal HSV is necessary for proper treatment and continuing management. Standard diagnostic tests include CSF PCR and swabs of any vesicular lesions. Serum for HSV PCR may be tested and is showing promising diagnostic value. Positive HSV cultures from non-CNS sites are diagnostic for neonatal HSV infection and remain the gold standard. Viral DNA detection by PCR assay is the gold standard diagnostic method for CNS disease (Kimberlin & Gutierrez, 2016).

Treatment. Early and consistent therapy with IV ACV has been determined to be the standard of care for all three presentation types of neonatal HSV infection. Because definitive results may take days to obtain, treatment must be begun when HSV infection has been suspected. There is convincing evidence that early therapy has the potential to decrease mortality and morbidity and improve long-term outcomes for infants with neonatal HSV infection (Allen & Robinson, 2014; Baley & Gonzalez, 2015; Kimberlin & Gutierrez, 2016). The recommended dose of ACV for neonates is 60 mg/kg/day in three divided doses given every 8 hours, if renal function is normal: for SEM disease, treatment is continued for 14 days. For disseminated or CNS disease, treatment should be continued for a minimum of 21 days, with weekly CSF sampling at the end of 21 days. ACV may be discontinued for suspected SEM disease when it is determined that the infant is not infected and after 21 days of treatment for the infant with CNS involvement who is shown to have negative CSF studies (Allen & Robinson, 2014; Stanberry, 2006). A topical agent should be administered along with ACV in neonates with eye disease (Kimberlin et al., 2018).

Prevention. Great progress has been made in surveillance for, and treatment of, neonatal HSV infection. However, the ideal approach to prevention is prevention of exposure of the fetus to the virus or the newborn to active maternal infection at the time of delivery. There is growing concern about transmission of the virus to unborn children with the concomitant increase in genital herpes as a sexually transmitted disease. Increases in risky sexual practices and the high incidence of HSV type 2 in the United States lead to increasing numbers of women of childbearing age who are at risk for newly acquired infection (Kimberlin & Gutierrez, 2016). The presence of maternal active HSV genital lesions or prodromal symptoms is a contraindication to vaginal delivery. If the membranes have been ruptured 4 hours or longer, cesarean section may or may not prevent transmission to the neonate. Daily use of oral antiviral prophylaxis with valganciclovir or ACV in the last trimester of pregnancy may reduce the risk to the infant and may reduce the number of elective cesarean sections (Baley & Gonzalez, 2015; Kimberlin & Gutierrez, 2016).

Quality and Safety: Postnatal nosocomial transmission is greatly reduced with good handwashing techniques and universal precautions. Hospitalized infected infants must be isolated because viral shedding provides a reservoir for infecting other infants in the nursery. HSV continues to be a life-threatening neonatal infection in the United States. It is important for all healthcare providers in the perinatal arena to maintain a high index of suspicion in infants whose symptoms may be compatible with HSV infection. Early identification allows prompt treatment or necessary continued observation, or both. Continued research may produce a more rapid method of virus identification and perhaps a safe and effective vaccine. Prevention of neonatal HSV depends on improved knowledge regarding the factors of virus transmission between mother and infant (Kimberlin & Gutierrez, 2016).

Primary nursing responsibilities in the management of a family with HSV infection are education and support. Mothers should be educated as to the mode, methods, and possible origins of the HSV, and concerns should be addressed regarding potential transmission to newborns. Nurses are often the first to document a mother's comment that she "had a small bump or blister and fever" right before her infant was born. **Quality and Safety: Careful history taking and thorough questioning can often identify potentially infected patients early.** With the diagnosis of genital herpes and subsequent monitoring procedures, families often feel stigmatized as well as anxious. Parents and responsible family members need education and support. Mothers with a history of genital HSV should be investigated for findings of active infection during the

peripartum period. Breastfeeding is contraindicated if the mother has a lesion on her breast. Infants are not isolated unless they themselves are infected. Many nurseries have guidelines regarding a 24- to 48-hour observation period to check cultures on an infant who was delivered vaginally through an infected genital area. An uninfected neonate does not require prolonged hospitalization, and, on discharge, the family needs information and education. Families should be informed that immediate medical consultation should be obtained with the development of major findings, including malaise, irritability, fever, temperature instability, respiratory distress, apnea, large abdomen or liver, sudden changes in skin color, new skin vesicles, lesions on the mucous membranes, or conjunctivitis. Sudden onset of systemic disease in a small, recovering preterm infant can include DIC and shock. Skin lesions are often absent in these severe cases, which may delay diagnosis (Kimberlin & Gutierrez, 2016).

All family members with active lesions anywhere on the body should be taught careful handwashing techniques to use before handling the baby. Any person with an oral HSV infection who handles the infant must wash well, wear a mask, and not kiss the infant anywhere until the lesions are completely crusted over and healed (Kimberlin & Gutierrez, 2016). The implementation of contact isolation provides healthcare workers as well as other patients with excellent protection against HSV infection in the workplace. Healthcare workers with active oral–facial lesions (cold sores) should take precautions, particularly when caring for high-risk patients such as newborns, immunocompromised individuals, and patients with chronic skin conditions (Stanberry, 2006).

Nonpolio Enteroviruses (EV). The genus *Enterovirus* consists of a broad range of viruses belonging to the family Picornaviride. The original classification system listed the EV into three main groups based on their replication patterns known at the time: Polioviruses, Coxsackieviruses (A & B), and Echoviruses (Abzug, 2014; Cherry & Krogstad, 2016). This section will focus on the nonpolio neonatal diseases caused by coxsackievirus A, coxsackievirus B, and echovirus.

Epidemiology. As the genus name implies, the GI tract is the main site for replication and source of transmission (Abzug, 2014). The EV have a worldwide distribution with seasonal prevalence in the more temperate regions (summer and fall). In tropical climates, there is year wide prevalence. The overall prevalence is difficult to estimate since the nonpolio viruses are not reportable and unrecognized infections mask the known numbers. Experts estimate EV disease incidence to be equal to or exceed that of GBS, HSV, and CMV (Abzug, 2014). Because of the seasonal occurrence, swimming pools may be a threat to children, who are the main susceptible group. Oral transmission is also possible through the air or by ingestion of contaminated materials or by contamination from objects in the environment. The incidence of infection and antibodies in general does not differ between males and females (Cherry & Krogstad, 2016). The human neonate is particularly susceptible in the first 2 weeks of life when associated with maternal illness and prematurity, with this unique group demonstrating a higher incidence in males. Prenatal and perinatal infection is also possible leading to infection of the neonate. The infant may present with typical signs of sepsis, although a wide variety of more serious findings may accompany EV infections (Modlin, 2015). The incubation period is typically 3 to 6 days, except for acute hemorrhagic conjunctivitis with an incubation period of 1 to 3 days. Infected children, both symptomatic and asymptomatic, frequently shed the virus from the respiratory tract for up to 3 weeks, whereas fecal shedding may continue for almost 3 months (Abzug, 2014).

Clinical Manifestations and Diagnosis. Although the majority of infants infected with EV may remain asymptomatic, those with severe disease have devastating disease with death or long-term sequelae resulting. It is important to emphasize that fatal infections account for only a small fraction of all congenital and neonatal EV infections. The most serious infections present with myocarditis, hepatitis, and encephalitis, with pneumonitis being seen less frequently (Modlin, 2015). Unfortunately, pathology reports are only available from postmortem examinations. Because of the similarity of presentation of EV infection with other viral, bacterial, and fungal infections, diagnosis cannot be made based on clinical findings alone, although suspicion may be increased based on time of year, exposure, incubation period, and certain clinical symptoms (Cherry & Krogstad, 2016).

Definitive diagnosis is made by detection of the virus from a variety of sources, including stool, rectal swab, CSF fluid, oral swabs, serum, and urine. PCR assays have a higher sensitivity than viral cultures and provide a quicker turnaround time (Abzug, 2014; Cherry & Krogstad, 2016).

Treatment. There are no approved definitive treatments for EV infections in the United States. Human immune globulin may be offered to infected infants in an effort to boost antibodies, although efficacy for acute illness has not been established. The antiviral drug pleconaril shows promise in neonatal EV infection. Serial studies have demonstrated important evidence that may lead to a treatment option. Pleconaril is not available for even compassionate use in the United States at this time. Supportive therapy is the mainstay of current treatment modalities. Infants who require intensive care may require respiratory support, cardiovascular agents, and eventually heart or liver transplants. Family support and involvement is needed with breastfeeding encouraged (Cherry & Krogstad, 2016; Modlin, 2015).

Prevention. As with any congenital or neonatal disease, elimination of the agent is the only way to eradicate the EV diseases. Vaccine development may be the best direction to follow globally. There has been a 99% reduction in infection with poliomyelitis, mostly because of vaccination, but the disease still exists. Infection control practices are in place and, with careful attention, should be effective in preventing outbreaks in hospital nurseries. When illness is detected, isolation and use of the cohort system is paramount (Cherry & Krogstad, 2016; Nikonov, Chernykh, Garber, & Nikonova, 2017).

Congenital Syphilis. Syphilis is a sexually transmitted disease caused by the bacterium *T. pallidum*. This bacterium is a gram-negative spirochete and is one of the few bacteria that can readily cross the placenta, resulting in fetal infection. Although most cases are the result of transplacental transmission, a few cases may result from contact with genital lesions during the delivery process (Baley & Gonzalez, 2015; Kollmann & Dobson, 2016).

Epidemiology. The World Health Organization (WHO) reports that more than two million pregnancies are complicated by syphilis annually and approximately two-thirds of those pregnancies end in poor outcome (Kollmann & Dobson, 2016). After reaching an historic low between 2000 and 2001, the national rate of syphilis has increased 17.6% to 8.7 cases per 100,000 population during 2015 to 2016. This increase is mostly attributable to sexual practices, particularly among gay and bisexual men (CDC, 2016).

Clinical Manifestations and Diagnosis. Untreated syphilis adversely affects pregnancy outcome. Vertical transmission of treponemas can occur at any time during pregnancy, with the likelihood increasing with advanced gestational age. The microorganisms can cause preterm labor, stillbirth, hydrops fetalis, congenital infection, or neonatal death. The incidence of congenital infection

where the mother was untreated or inadequately treated is highest during the 4-year period following acquisition of primary infection, secondary infection, and early latent disease. When newborns acquire syphilis from hematogenous spread across the placenta, the effects are on the major organ systems of the fetus, especially the CNS. Common presentations of the infected infant are hepatosplenomegaly, jaundice, LBW, intrauterine growth restriction, snuffles, mucocutaneous lesions, anemia, and osteochondritis. There is often a bilateral superficial peeling of the skin (desquamation) on the neonatal palms and soles. Nonimmune hydrops is a common presentation in congenital syphilis. The symptoms of perinatal syphilis are similar to those of any other viral infection that spreads hematogenously from the mother to the placenta and on to the developing fetus (Kimberlin et al., 2018; Kollmann & Dobson, 2016).

The serological status of all women who deliver in a hospital should be determined before the newborn is discharged (Kimberlin et al., 2018). All infants born to seropositive women require, at a minimum, careful physical examination and a nontreponemal test such as the Venereal Disease Research Laboratory (VDRL) slide test and the rapid plasma regain (RPR) test. In the event of a positive nontreponemal test or abnormal neonatal physical examination, further testing, such as chest radiograph, eye examination, liver function tests, neuroimaging, and auditory brainstem response, is required. Because an infant's RPR/VDRL will be positive if born to a RPR/VDRL-positive woman, the titers are more diagnostic than the positive result. The infant's quantitative nontreponemal test is considered significant if the titers are fourfold (or greater) higher than the mothers. A test positive at two dilutions is the same as a fourfold increase. An LP for CSF analysis (including quantitative VDRL) and radiographs of the long bones can further the definitive diagnosis of syphilis in the neonate and should be performed in all cases of probable congenital syphilis. Radiologic changes such as osteochondritis (a blurring of the epiphyseal borders) demonstrate recent fetal infection and periostitis represents prolonged involvement, probably within 16 weeks or second trimester infection (Kimberlin et al., 2018; Kollmann & Dobson, 2016).

Treatment. The recommended treatment for a newborn presumed to be infected with congenital syphilis is aqueous penicillin G. Treatment plans are based on whether the infant is suspected to have or is proven to have congenital syphilis. Treatment guidelines are available on the CDC website (www.cdc.gov/std/syphilis/treatment.htm) and in the 2018 AAP Red Book (Kimberlin et al., 2018). A newborn with an antibody titer four or more times higher than the maternal level should be treated as if a definitive diagnosis has been obtained. For proven or highly probably congenital syphilis, aqueous crystalline penicillin G, 50,000 U/kg, given intravenously every 12 hours for the first week and then every 8 hours after the first week for a total of 10 days is the preferred treatment. When the IV route is not feasible, procaine penicillin G, 50,000 U/kg, intramuscularly (IM) as a single daily dose for 10 days is acceptable. For asymptomatic infants whose mothers were treated adequately during pregnancy, treatment is not necessary unless follow-up cannot be ensured. Some clinicians recommend a single dose of benzathine penicillin: 50,000 U/kg IM, if the infant is not likely to be followed up on. If maternal treatment did not include penicillin and if neonatal follow-up is likely to be unreliable, the neonate is given a full 10-day course (Kimberlin et al., 2018; Kollmann & Dobson, 2016).

Emergency Alert: It is imperative for the physician or nurse practitioner (NP) writing the order for penicillin to be clear on the form of penicillin to use. Aqueous crystalline penicillin G is approved for IV usage. Benzathine penicillin G and procaine penicillin G can only be administered IM. IV administration may cause life-threatening side effects or death.

Isolation of an infant with suspicious symptoms may be necessary until appropriate treatment is given. There is a definite role for nursing education and support in the treatment of an infant exposed to syphilis. The 10-day course of penicillin treatment may lead to the establishment of a trusting relationship between the nurse and family, thus providing an opportunity to give more information regarding sexual risk factors. Families often need encouragement and support to get treatment for other sexual partners and to obtain other necessary medical evaluations (such as HIV screening or drug counseling).

Prevention. Prevention of congenital syphilis is accomplished by prevention of syphilis in childbearing women. Identification and adequate treatment of pregnant women is necessary. Infants with confirmed congenital syphilis should receive careful follow-up evaluations. Regular childhood well-child visits should be ensured. Serologic nontreponemal measurements can be made at follow-up visits with their primary care physician (Kimberlin et al., 2018). In the infant with congenital neurosyphilis, CSF examinations should be done every 6 months, with retreatment as needed, until the studies are normal. The infection can be effectively treated, but the physiologic and developmental prognosis depends on the degree of organ damage sustained during fetal development.

Other Sexually Transmitted Diseases

Gonorrheal Ophthalmia. Ophthalmia neonatorum is the result of infection of the mucous membranes by *Neisseria gonorrhoeae* or *Chlamydia trachomatis;* these infections may be found simultaneously. Neonatal conjunctivitis caused by *N. gonorrhoeae* is the primary concern when maternal gonorrhea has been diagnosed. Although infection of mucosal surfaces is more common in the infant born to an infected mother, scalp abscesses and systemic infection can occur (Embree, 2016).

Epidemiology. *Neisseria gonorrhoeae* is a species of small gram-negative diploid bacteria. Infection with this organism is seen most frequently in young adults less than 24 years of age. Other risk factors include unprotected sex, multiple sex partners, drug and alcohol abuse, and low-income status. In the United States, rates are higher in the non-white communities. In the United States, there were 104.1 cases per 100,000 population in 2011 (Embree, 2016). *Neisseria gonorrhoeae* is the second most reported of sexually transmitted diseases, exceeded only by *C. trachomatis* (Kimberlin et al., 2018). In females, infection may be asymptomatic, which compromises detection of the disease. Neonatal gonococcal conjunctivitis is known to occur in 30% to 40% of cases where maternal cervical infection is present (Leonard & Dobbs, 2015). The incubation period is typically 2 to 7 days; however, gonococcal infection should be considered in any infant with conjunctivitis present after 24 hours of birth (Embree, 2016).

Clinical Manifestations and Diagnosis. Gonococcal conjunctivitis in the newborn has historically been a risk from transmission via the birth canal. Although asymptomatic colonization has been reported, typically the infected infant presents with acute purulent conjunctivitis and edema of the eyelids. Other possible neonatal findings include scalp infection or systemic manifestations including pneumonia, sepsis, osteomyelitis, or meningitis. Untreated, the illness may spread to the connective tissues and cornea (Embree, 2016).

Although conjunctivitis may be obvious based on clinical signs, definitive diagnosis is necessary in planning the management and treatment. Ophthalmia neonatorum from other organisms must be differentiated from conjunctivitis from other organisms. Gram stain of the drainage will reveal the gram-negative diplococcic typical of *N. gonorrhoeae*. This provides a presumptive diagnosis. If Gram stain is positive, cultures should be obtained of the eye drainage as well as from additional mucosal sites in the infant.

Testing of the mother and her sexual partner is essential. Specifics for testing of adults is beyond the scope of this chapter on neonatal illnesses but is a prerequisite for management and treatment of the newborn (Darville, 2016; Embree, 2016).

Treatment. Infants who are delivered to an infected, untreated mother are usually given a complete infection workup, including an LP, and given a single dose of ceftriaxone. Globally, *N. gonorrhoeae* is increasingly resistant to penicillin; therefore, this antibiotic is no longer recommended, unless the specific isolate has been proven to be sensitive. If cultures confirm the presence of the microorganism, the infant should be treated with ceftriaxone, 25 to 50 mg/kg/day (maximum of 125 mg) IV or IM in a single dose for 7 days (10–14 days if meningitis is confirmed). Cefotaxime is recommended for infants with hyperbilirubinemia, especially if born prematurely, because ceftriaxone competes for bilirubin binding sites on albumin (Darville, 2016; Embree, 2016). For gonococcal ophthalmia neonatorum, a one-time single dose of ceftriaxone is recommended to prevent progression to corneal ulceration and/or perforation (Kimberlin et al., 2018). Irrigation of the eyes with a normal saline solution frequently, until drainage is no longer seen, is also an important addition to the management plan. This practice has been shown to decrease long-term consequences. Addition of ophthalmic antibiotic drops has not been shown to improve outcome and is not deemed necessary. Education and support regarding the origin of the infectious agent are important in the treatment of gonorrhea. Sexual partners of infected persons should be encouraged to seek testing and appropriate antibiotic treatment for gonorrhea (Embree, 2016; Kimberlin et al., 2018).

Prevention. Use of silver nitrate solution or erythromycin for the prevention of gonococcal ophthalmia neonatorum is one of the early achievements in preventive medicine. Silver nitrate was discontinued due to the universal development of chemical conjunctivitis. Routine prophylaxis is mandated by law in the United States and has made a significant difference in the treatment of ocular disease if administered within 1 hour of birth. Erythromycin ointment in both eyes is a well-established and efficacious prophylactic practice for the prevention of gonococcal ophthalmia (Embree, 2016). Chlamydia conjunctivitis has become far more common than gonococcal conjunctivitis in the neonate because of the continual screening for gonorrhea.

Chlamydia Conjunctivitis. *Chlamydia* is a genus of intracellular bacteria that may affect virtually all animal species. Although the genus *Chlamydia* is divided into at least four groups, this chapter will focus on the organism *C. trachomatis*. *Chlamydia trachomatis* infection is the most common sexually transmitted disease. Maternal infection may lead to neonatal conjunctivitis and chlamydia pneumonia. Neonatal conjunctivitis can be expected in 30% to 50% of infants born to infected but untreated mothers. Pneumonia caused by *C. trachomatis* will develop in 10% to 20% of newborns of women with active, untreated chlamydia infection. Conjunctivitis will be the focus of this section.

Epidemiology. *Chlamydia trachomatis* is the most common sexually transmitted disease in the Western industrialized nations. Most infected men and women are asymptomatic, leading to underestimation of the prevalence. This is a worrisome fact since this could theoretically support a large reservoir within our societies that can sustain the pathogen. Risk factors are the same as for other sexually transmitted diseases—young age (<20 years), socioeconomically disadvantaged, geography, and number of sexual partners. The infection can present in women as cervicitis, salpingitis, urethritis, or pelvic inflammatory disease. *Chlamydia trachomatis* infection has been identified as causing a significant increase in the incidence of PROM, the number of LBW babies, and the rate of infant mortality (Darville, 2016). Thus, screening pregnant women for chlamydia is an essential part of prenatal care.

Clinical Manifestations and Diagnosis. Chlamydia conjunctivitis can present in the newborn with a very watery discharge that may progress to purulent exudate. The incubation period is anywhere from 5 to 14 days but may be shorter in cases of prematurely ruptured membranes. Prior to treatment, the eyelids may swell and a "pseudomembrane" consisting of inflammatory excaudate may form and stick to the conjunctiva (Darville, 2016).

Diagnosis of chlamydial infections is based on physical and laboratory examination. In cases of conjunctivitis, Giemsa-stained conjunctival scrapings provide a method of direct fluorescent antibody (DFA) testing. This method is the only Food and Drug Administration (FDA)-approved culture-independent method for detecting chlamydia from conjunctival swabs. The organism is not detectable on routine Gram stains. Cell culture demonstrates high specificity but is expensive. The definitive diagnosis for chlamydial pneumonia is made by culture of the respiratory tract or identification of high levels of IgM antibodies to chlamydia (Darville, 2016; Kimberlin et al., 2018).

Treatment. Universal eye prophylaxis with antibiotics is required by law in the United States for every newborn. Application of erythromycin ointment at birth for ocular prophylaxis successfully treats gonococcal conjunctivitis but has not been as successful in treating chlamydial conjunctivitis. Even for infants born to mothers known to have untreated chlamydial infection, prophylactic antimicrobial treatment is not indicated due to the unknown efficacy of such treatment. In these cases, the infants should be monitored clinically with appropriate diagnostic workup and appropriate treatment if the infant becomes symptomatic (Kimberlin et al., 2018). The treatment of highly suspected chlamydia infection in the newborn usually begins with ampicillin and gentamicin if the infant's workup is for generic infection. Once the chlamydia organism is identified, treatment with "oral erythromycin base or ethylsuccinate (50 mg/kg/day in 4 divided doses daily) for 14 days or with azithromycin (20 mg/kg as a single daily dose) for 3 days" is recommended (Kimberlin et al., 2018, p. 280). In the case of neonatal conjunctivitis, topical therapy in addition to systemic treatment is indicated. Follow-up of infants treated for chlamydial conjunctivitis is recommended to determine if treatment was effective. If chlamydia is confirmed in a pregnant woman and treated, her sexual partners also require treatment. This organism may be present for many years in the female genital tract and produce no symptoms. The organism does not respond to partial treatment; an infected woman and all her sexual partners must receive full treatment as soon as possible (Darville, 2016).

Prevention. Prevention of sexually transmitted diseases is the same regardless of the organism in question. The only definitive method of prevention is screening and treating the infected pregnant woman. Education and counseling regarding the method of transmission of chlamydia are important. This organism may be present for many years in the female genital tract and produce no symptoms. The organism does not respond to partial treatment; an infected woman and all her sexual partners must receive full treatment as soon as possible. Men should wear condoms during sexual relations to prevent transmission. Without treatment, the severe complications for the woman include pelvic inflammatory disease, ectopic pregnancy, and endometritis (Darville, 2016).

Varicella-Zoster. Varicella is a member of the human DNA herpes viruses. Primary infection with the VZV causes chickenpox. This primary infection is followed by a lifelong period of latent infection of the sensory ganglion neurons. Herpes zoster (shingles) may develop later in life in those who had varicella, especially the elderly and

those with immune deficiency. Chickenpox is extremely contagious and commonly occurs in childhood. Varicella is known as the most communicable of all diseases and is only found in humans (Gershon, Marin, & Seward, 2016; Kimberlin et al., 2018; LaRussa & Marin, 2016). Because of the devastating effects of congenital varicella syndrome (CVS), varicella will be the focus of this section.

Epidemiology. The incidence of this virus in pregnant women is very low, approximately in the range of 0.5 in 10,000 pregnancies, mostly due to success of the varicella vaccine. Transmission of the virus is by direct contact with the virus in vesicular lesions or by airborne droplet spread via the respiratory tract. Symptoms of varicella are usually present 10 to 21 days after exposure and include fever, malaise, and an itchy rash. Administration of varicella-zoster immune globulin (VZIG) may delay onset for up to 28 days. An infected individual is considered contagious from 1 to 2 days before onset of symptoms until all lesions have crusted. The maculopapular rash eventually forms vesicles and crusts over at around 6 days after onset (Baley & Gonzalez, 2015; Gershon et al., 2016; Kimberlin et al., 2018). In utero infection occurs as a result of transplacental passage of the virus during gestation in the infected mother. The severity of the effect on the fetus or newborn is related to the timing during gestation. The lowest risk of CVS occurs when the mother is infected during the first trimester and rises slightly during weeks 13 through 20. CVS rarely occurs after the 20th week of gestation. There is a higher case-fatality rate in offspring when illness develops in the mother from 5 days before to 2 days after birth of the infant. The severity of CVS is decreased when varicella develops in the mother more than 5 days before delivery and after 28 weeks' gestation. It is thought that maternal transfer of varicella-zoster–specific IgG is responsible (Kimberlin et al., 2018).

Clinical Manifestations and Diagnosis. CVS is characterized by cicatricial skin lesions with scarring, limb hypoplasia, CNS involvement, and abnormalities of the eye, renal system, and autonomic nervous system. Neonatal death is most often the result of pneumonia (Baley & Gonzalez, 2015; LaRussa & Marin, 2016).

In the neonate, identified infection in the mother will easily lead to a diagnosis of CVS when clinical manifestations are obvious, such as a widespread vesicular exanthema. A similar presentation is more difficult to identify when there is no known maternal infection. The definitive diagnosis of varicella is made by identification of VZV from vesicular fluid using a PCR test. Other methods are available but the PCR assay is the diagnostic method of choice. Culture and DFA testing are less sensitive and, therefore, unreliable. The presence of specific IgM may only indicate recent exposure or infection and is not a reliable indicator for CVS (Baley & Gonzalez, 2015; Kimberlin et al., 2018).

Treatment. Although there are those who believe that the consequences of CVS do not progress in severity after birth, ACV can be used for treatment of severe disease in newborns, whether congenital or postnatally acquired. The recommended dosage for immunocompromised host less than 2 years of age is 30 mg/kg/day for 7 to 10 days (Kimberlin et al., 2018). There is a limited window for best outcome with antiviral therapy for varicella. Early therapy maximizes benefit. VZIG can be given to newborns to decrease the severity of infection in those exposed and should be administered within 96 hours of exposure (Baley & Gonzalez, 2015; Kimberlin et al., 2018). **Emergency Alert: Children with varicella should not be given salicylate or salicylate-containing products (aspirin, bismuth subsalicylate). These products are known to increase the risk of Reye syndrome.**

Prevention. The primary approach to prevention of CVS is vaccination of women of childbearing age before pregnancy. Although not 100% effective, vaccination could protect 85% of women, and, therefore, their infants. Strict isolation of identified infants or of those whose symptoms are highly suspicious for infection is necessary. Infants should be vaccinated according to established vaccination schedules. Hospitals should initiate and strictly enforce guidelines for maintaining immunity of hospital personnel. Isolation for airborne and contact illnesses should be followed. Typically, if a mother has contracted varicella infection late in pregnancy, other persons, such as healthcare workers, family members, or other newborns, may have been exposed (Gershon et al., 2016). In cases where the mother was infected during pregnancy, and the infant does not show evidence of disease at birth, the mother and infant should be isolated separately until the mother's lesions have crusted over. If the infant develops clinical evidence of disease, the mother may care for the infant if she is well enough. Isolation should continue during hospitalization and after discharge for a total of 21 days (28 days if IVIG was given; Kimberlin et al., 2018).

VZIG can be given to newborns to decrease the severity of infection in those exposed; it does not prevent infection. If exposure occurs within a neonatal intensive care unit (NICU), it is recommended that if there is risk of significant exposure (such as in an open bed environment as opposed to single room environment) all premature infants less than 28 weeks or less than 1 kg receive VZIG regardless of maternal immunity status as there has been inadequate transfer of maternal antibodies. VZIG should also be given in the NICU setting when there is significant exposure in the 28th week of gestation or more and in neonates with maternal seronegative immunity status (Kimberlin et al., 2018).

Lyme Disease.

Lyme disease is the most common vector-borne disease in the United States. It is caused by the spirochete *B. burgdorferi*. Lyme disease is transmitted to humans by the bite of the blacklegged tick, commonly known as the deer tick. Because other spirochetes are known to cause significant, and often devastating, outcomes, when transplacental infections occur, the risk of disease in the newborn from Lyme disease is of considerable interest (Feder, 2016).

Epidemiology. Lyme disease has been identified in more than 50 countries. In the United States, in excess of 30,000 cases are reported to the CDC each year. It is known that this is only a proportion of the actual cases. The CDC estimates that the number of people diagnosed may be around 300,000. There is a concentration of cases in the Northeast and Upper Midwest, with 14 states accounting for over 96% of reported cases (CDC, 2018). Tick larvae become infected by feeding on animals that are infected. The nymphal stage is the stage most likely to infect humans with the spirochete. This stage emerges in the spring to early fall, when deer activity is greatest, making this season the most likely time for humans to become infected. Evidence indicates that the risk of Lyme disease after a deer tick bite is only 1% to 3%. Late disease, mainly arthritis, occurs at any time. Although infection can occur at any age, the reported incidence is greater in children from 5 to 9 years of age, with a second peak occurring in middle-aged adults (Eppes, 2016; Feder, 2016).

Clinical Manifestations and Diagnosis. In adults, clinical manifestations can be divided into early (early localized or early disseminated) disease or late disease. Early-localized disease is characterized by a distinct lesion at the site of a recent tick bite, although the person may not be aware of having been bitten by a tick. There is a classic "bull's eye" appearance in some, but not all, cases. There may be an accompanying clinical presentation of extreme tiredness, headache, mild neck stiffness, muscle pain, and maybe fever. In early-disseminated disease, multiple lesions of erythema migrans may appear 3 to 5 weeks after the tick bite. These lesions are smaller but similar to the primary lesion. There may be palsies

of the cranial nerves, lymphocytic meningitis, and rarely carditis. The signs of early-localized disease can be expected as well. Late Lyme disease occurs in people who were not treated early in the disease and most commonly presents in Lyme arthritis in children who were not treated (Eppes, 2016; Kimberlin et al., 2018).

In areas where Lyme disease is endemic, transplacental infection is known to occur, although congenital infection is rare. There are case reports of fetal loss and newborns with anomalies. Although skin anomalies and cardiac defects have been noted in infants born to mothers with Lyme disease, the inconsistency in findings suggests that there is no recognized syndrome associated with fetal infection. Attempts to investigate the significance of gestational Lyme disease on the newborn have been limited. First, the prevalence is low and, second, diagnosis based on current methods of seropositivity, history of tick bite, and reports of clinical symptoms in the mother is unreliable. Because of increased awareness of the problems associated with Lyme disease, most childbearing women are being identified and treated, especially if pregnancy is suspected. *Borrelia burgdorferi* has been identified from several abortuses and from a few live born children with congenital anomalies. Furthermore, evidence suggests that there is no difference in the prevalence of congenital malformations in infants born to women with serum antibodies against *B. burgdorferi* and the offspring of those without such antibodies (Eppes, 2016; Feder, 2016). The CDC currently recommends a two-step process in the testing for evidence of Lyme disease. These steps can be done together, using the same blood sample. The first step uses an EIA or enzyme-linked immunosorbent assay (ELISA). Rarely, an indirect immunofluorescence assay (IFA) is used. If this first step is negative, no further testing of the specimen is recommended. If the first step is positive or equivocal, the second step should be performed. The second step consists of the Western immunoblot (Western blot). Results are considered positive only if both steps render a positive result. The two steps of Lyme disease testing are designed to be done together. Skipping the first step is not recommended due to many false-positive reports (APA, 2018k; CDC, 2018).

Treatment. Current treatment protocols include an oral regimen of doxycycline, amoxicillin, or cefuroxime axetil. Doxycycline is not recommended for use in young children under the age of 2 years due to reports of permanent teeth staining. All persons receiving doxycycline should be warned of the side effect of photosensitivity in sun-exposed areas. Early use of appropriate antibiotics is associated with rapid and complete recovery. People with certain neurologic or cardiac forms of illness with neurologic or cardiac involvement may require IV treatment with ceftriaxone or penicillin (CDC, 2018; Eppes, 2016).

Prevention. Reducing the risk of tick bites is the only definitive preventive measure. Methods to reduce the risk involve decreasing the known habitat of the deer tick. Keeping yards clear of brush and frequently mowed may reduce exposure in endemic areas. Pesticides may be effective in reducing the tick population, but many unwanted and undesirable side effects are inherent in their usage (Feder, 2016).

Human Immunodeficiency Virus. HIV is one of the greatest public health concerns of the past three decades and remains so in the 21st century. Both HIV-1 and HIV-2 are RNA-containing retroviruses of the Retroviridae family and belong to the *Lentivirus* genus (Kimberlin et al., 2018). Retroviruses are characterized by the presence of a viral reverse transcriptase enzyme that converts single-stranded viral RNA into double-stranded DNA. This double-stranded DNA copy integrates into the host cell genome. Because HIV-1 is more prevalent in the United States, HIV-1 will be the focus of this section, especially as it affects the newborn.

Epidemiology. Although a virus very closely related to HIV was originally identified in chimpanzees and monkeys in Africa, it has long been known that HIV affects humans, attacking cells containing the surface molecule, $CD4^+$, particularly T lymphocytes and macrophages. Originally thought to be a disease mainly affecting men who have sex with men (MSM), HIV is now known to occur in both men and women and in children. HIV is no respecter of socioeconomic status, gender, age, or nationality; however, disparities still exist. Sub-Saharan Africa is devastated by the epidemic with 69% of HIV infections or approximately 23.5 million people infected by HIV. China follows sub-Saharan Africa, with 4 million infected, and then the Americas (including the Caribbean), with 3 million HIV-infected people. HIV often leads to AIDS in the untreated patient and may advance to AIDS despite treatment. Chronic immune activation, with depletion of $CD4^+$ cells, via the adaptive and innate immune systems, plays an important role in the immunopathogenesis of HIV/AIDS. The good news is that rates are declining, with the most significant declines noted in the Caribbean and sub-Saharan Africa (Kimberlin et al., 2018; Shetty & Maldonado, 2016). The only epidemiologically implicated ways of transmission are through contact with blood, semen, cervicovaginal secretions, and human milk (Kimberlin et al., 2018). Mother-to-child transmission has declined dramatically, due to early recognition and treatment of women of childbearing age; therefore, there is a relatively stable incidence of infection. Although rates are declining, the incidence is still unacceptable. The vast majority of children living with HIV are infected as a result of vertical transmission from an HIV-infected mother. In utero infection occurs through transplacental infection or by fetal exposure of infected amniotic fluid. Current data suggest that in utero infection occurs during the last few weeks of gestation when placental vasculature is proliferative. Intrapartum infection may be the result of direct exposure of the fetus or infant with infected maternal secretions or exposure to maternal blood during labor (Shetty & Maldonado, 2016). Although maternal-to-child transmission occurs across a large range of viral loads, maternal viral load is the most critical determinant of maternal transfer of the virus. The risk increases with ROM and increases in a direct relationship to the time of ROM. Cesarean delivery before ROM is known to reduce maternal-to-child transmission. Postnatal transmission is most likely the result of breastfeeding as prolonged breastfeeding is a common practice in low-to-middle-income families, where safe alternatives to feeding the infant may not be available or may be unsafe (Kimberlin et al., 2018; Shetty & Maldonado, 2016).

Clinical Manifestations and Diagnosis. Perinatal HIV infection results in a wide variety of manifestations and depends on the stage at diagnosis. Most HIV-infected newborns are asymptomatic at birth because infection most likely occurs during the peripartum period. Clinical signs typically begin to manifest around age 1 or 2. For some poorly understood reason, there are some infants, termed rapid progressors, who may become symptomatic in the first 2 months (Baley & Gonzalez, 2015). In the untreated pediatric population, early clinical signs include fevers of unknown cause, lymphadenopathy, enlargement of the liver and spleen, failure to thrive, persistent candidiasis, diarrhea, encephalopathy, either hyporeflexia or hyperreflexia, and developmental delays. Recurrent opportunistic infections are common and may increase the risk of death (Kimberlin et al., 2018). Prognosis for survival for the neonate, infant, or child infected with HIV is based on timing of infection and treatment modality. Death in untreated infants is invariable.

Unless assay results are negative, antibody assays are not helpful in the diagnosis of HIV in children under the age of 24 months because these infants and toddlers will have maternally acquired passive antibodies. These maternal antibodies make the EIA, Western blot, inappropriate in infants up to 18 to 24 months of age. Currently,

in the United States, the most sensitive and, therefore, the most preferred test is the HIV DNA PCR or RNA assay, referred to as HIV nucleic acid amplification tests (NAATs). If the test becomes positive within 48 hours of birth, in utero transmission is assumed (Kimberlin et al., 2018; Shetty & Maldonado, 2016). Some experts recommend viral testing in the first 2 days of life for all infants suspected to have in utero infection to increase the chance of early identification and treatment. Umbilical cord testing is not acceptable due to the possibility of contamination with maternal blood. Refer to the AAP Report of the Committee on Infectious Diseases, 2018, Redbook, for an algorithm for interpreting the test results (Kimberlin et al., 2018).

Treatment. It is important to know that treatment with antiviral therapy does not cure HIV; instead, it suppresses the virus with the goal of converting the active disease to a chronic disease. Because of the options available for treatment of HIV-infected infants and children, consultation with an expert in pediatric HIV infection is the standard of care for these individuals (Kimberlin et al., 2018). The most important factor in the outcome for infants exposed to or infected with HIV is whether or not the mother received antepartum/intrapartum antiretroviral therapy (ART) and her viral load. Maternal treatment is not the purpose of this section but whether or not, and when, the mother received treatment is paramount in the decisions around treatment of the infant. ART resistance is becoming more evident and treatment protocols change with current findings. The newborn infant, exposed to HIV in utero, should be bathed as soon as possible after birth to remove all blood and maternal secretions. Antiretrovial (ARV) prophylaxis should be started as early as possible, preferably within 12 hours after birth. Current treatment guidelines may be found online at: https://aidsinfo.nih.gov/guidelines. Enrollment of HIV-infected infants in clinical trials may provide opportunities for exposure to the newest treatment modalities (Kimberlin et al., 2018).

Prevention. Theoretically, prevention of HIV in adults and adolescents can be accomplished by safe sexual practices, limiting exposure to HIV-infected blood, and education to all sexually active individuals about the risk factors and ways to avoid them. Prevention of HIV transmission to the infant has been the focus of research since the first recognition of maternal-to-infant transmission. The result has been the use of ART for the pregnant woman with known HIV infection. Current recommendations are that all pregnant women are tested early in pregnancy and ARV therapy begun. Increased research effort on adherence to recommendations and how they affect youth are needed.

Parvovirus.

The parvoviruses are a family of small, single-stranded DNA viruses of the family Parvoviridae. The parvoviruses are animal viruses and seem to be species specific. Parvovirus B19 is the member that replicates in humans and is known to be a pathogen. Bocavirus has been recently recognized as a human parvovirus but only infects children. Parvovirus B19 will be the focus of this section (Baley & Gonzalez, 2015).

Epidemiology. The human parvovirus, B19, often referred to as "fifth disease," is a common and highly contagious pathogen around the world. The majority of adults in the United States are seropositive, indicating a previous infection during childhood. The incidence is twice as high in Caucasian Americans as in African Americans. The virus is transmitted mainly by droplets from oral or nasal secretions but can also occur from percutaneous exposure to blood or blood products (Kimberlin et al., 2018). Rapid transmission occurs due to close contact between family members or school classmates (Adler & Koch, 2016).

Clinical Manifestations and Diagnosis. The focus of this chapter is on the effects of disease on the neonate; therefore, this section will discuss the clinical manifestations and diagnostic tests necessary when an infant is suspected of having Parvovirus B19. There have been reports of serious, and often devastating, outcomes for the fetus and newborn when the mother has primary infection of Parvovirus B19. Adverse outcomes include hydrops fetalis, isolated pleural or pericardial effusions, intrauterine growth restriction, and intrauterine fetal demise. Although poor outcomes are possible, the infected neonate will likely be asymptomatic at birth. The risk of maternal-to-infant transmission is low (≤10%); the greatest risk occurs with maternal infection during the first 20 weeks of gestation. Other reported fetal outcomes from maternal Parvovirus B19 infection include occasional birth defects (ocular defects), although this finding could not be attributed to the virus in repeated studies. Meconium ileus and peritonitis have also been reported in neonates following maternal infection during pregnancy (Adler & Koch, 2016; Baley & Gonzalez, 2015).

The diagnosis of Parvovirus B19 in the newborn infant is based on identification of the infection in the mother. Most infants are asymptomatic at birth and rarely require virologic confirmation. The preferred diagnostic tests for acute or recent Parvovirus B19 is detection of serum-specific IgM antibodies. Prenatal diagnosis, when fetal hydrops is suspected, can be verified by detection of viral DNA in fetal blood or amniotic fluid by these methods (Kimberlin et al., 2018; Koch, 2016).

Treatment. Treatment for the prenatally infected infant is based on clinical manifestations, if present. Fetal transfusion may be indicated in cases of hydrops fetalis with significant fetal anemia. Several separate transfusions may be necessary for resolution of the hydrops. Each transfusion is associated with an increase in risk to the fetus; however, the benefit certainly exceeds the risk (Adler & Koch, 2016).

Prevention. Pregnant healthcare providers should be informed of the potential risks to their fetus from Parvovirus B19 infections. The best strategy to decrease the risk of infection is to pay attention to strict infection control procedures including standard precautions and droplet precautions if the hydrops has not resolved in the neonate at the time of birth (Kimberlin et al., 2018).

Other Viruses

Hepatitis B Virus. The hepatitis B virus (HBV) is a fairly large, double-stranded DNA–containing virus in the family Hepadnaviridae. Hepatitis B surface antigen (HBsAg) is present in the chronic carrier state. A chronic carrier state is defined as persistence of the HBsAg in serum for at least 6 months (AAP, 2018g).

Epidemiology. HBV has been detected worldwide, with an estimated 400,000 persons known to be chronic carriers. In the United States, the prevalence of HBV infection in pregnant women shows a distinct disparity by race and ethnicity, with the highest rates reported in Asian women; rates in African American, Caucasian, and Hispanic women are similar with the lowest rates in Hispanic women. Chronic HBV infection is endemic in sub-Saharan Africa, China, parts of the Middle East, the Amazon basin, and the Pacific Islands. In these areas, carrier rates are estimated to be 35%. In the United States, where a successful vaccination program exists, there are still an estimated 1.25 million chronic HBV carriers (Jensen & Balistreri, 2016; Karnsakul & Schwarz, 2016). The primary route of transmission is through infected blood or bodily fluids. The surface antigen, HBsAg, has also been noted in human milk, saliva, and tears. Blood, serum, semen, vaginal secretions, CSF, and other bodily fluids, such as synovial, pleural, pericardial, peritoneal, and amniotic fluid, present the most potential for transmission of the virus. Transmission by blood or blood products in the United States has been virtually eliminated due to routine screening of donors (AAP, 2018g). HBV infection in a pregnant woman does not appear to have teratogenic abilities, although there are reports of a higher incidence of LBW and prematurity. Acute HBV infection in the mother early in pregnancy has a 10% transmission rate with a higher incidence when acute infection occurs in the third trimester.

Chronic infection in the pregnant woman does not appear to have an effect on pregnancy outcome (Karnsakul & Schwarz, 2016). HBV is most often the result of IV drug use but transmission also occurs through sexual contact with an infected partner and via mother-to-infant transmission. The majority of infections from mother to infant occur at birth or in the postpartum period. A large percent of infants born to mothers with a high viral load develop chronic HBV infection (Baley & Gonzalez, 2015).

Clinical Manifestations and Diagnosis. Clinical manifestations of HBV infection are age dependent. In the adult, HBsAg is detected 1 to 3 months after exposure to the virus. Elevation of liver enzymes occurs between 2 weeks and 2 months after detection of HBsAg. The symptoms most often reported are nausea, vomiting, headache, and lethargy. This period progresses to the development of jaundice. Most adults with HBV infection have a self-limited course. A few will develop hepatic failure and many of these will die. A chronic carrier state, or persistent HBV infection, is also possible. In the United States, 20% to 30% of all cases of chronic infection are in children. Chronic liver disease and hepatocarcinoma may result from a chronic carrier state (Baley & Gonzalez, 2015; Jensen & Balistreri, 2016).

Ninety percent of infants born to women who are positive for both HBsAg and hepatitis B e antigen (HBeAg) are at risk for development of HBV infection by their first birthday if they are not given treatment. Infants born to women who are positive for HBsAg but negative for HBeAg have lower rates of perinatal infection (20%). Infants who do not receive treatment are likely to become carriers, which may eventually lead to cirrhosis or primary hepatocellular carcinoma. A few (6%) may develop acute hepatitis at around 2 months of age. Symptoms most reported for infants are fever, jaundice, and hepatic tenderness. Serum aminotransferases are elevated (Karnsakul & Schwarz, 2016).

The serologic diagnosis of HBV is complex and is different depending on whether the disease is acute or chronic. HBsAg is used to detect acutely or chronically infected people. HBsAg is an important test in assessing a woman's risk of transmitting HBV to her unborn child. HBeAg is used in the identification of people who are at the greatest risk of transmitting the virus. The presence of HBsAg and HBeAg is the best indication of infectiousness. It is currently recommended that all pregnant women be screened at their first prenatal visit for HBsAg and HBeAg to prevent prenatal transmission; for high-risk populations, this should be repeated in the third trimester (Jensen & Balistreri, 2016).

Treatment. Hepatitis B vaccine is the golden standard for prevention of HBV. All infants should receive the first vaccine before discharge from the birth hospital, preferably within 24 hours of birth. Infants born to mothers who are at risk of transmitting the virus should receive the HBV vaccine along with hepatitis B immunoglobulin. An algorithm exists for determining the timing and dosage for infants according to birth weight as well as for prophylaxis according to maternal HBV status (AAP, 2018g; Baley & Gonzalez, 2015). Vaccination is recommended for individuals who are at risk for exposure to HBV, including healthcare workers, family members of chronic carriers, persons with large numbers of heterosexual partners, and IV drug users. Hep B vaccine is administered to the deltoid muscle once and then again 1 and 6 months later (AAP, 2018g).

Prevention. Proper and prompt identification of women in high-risk groups and knowledge of HBV status are important in the delivery room to determine whether the infant is at risk for infection. In accordance with universal infection control measures, appropriate barriers are used to protect healthcare workers from blood and body secretions. Delivery room and nursery personnel should always wear gloves when handling any new infant. The infant of a mother with confirmed HBV infection should be bathed with soap and water immediately, with special attention to removing all blood and secretions present on the skin and hair. The infant may be breastfed (unless the mother's nipples are cracked) and cared for routinely. Family clustering of HBV has been identified and spread via household contact (AAP, 2018g; Baley & Gonzalez, 2015).

Fungal Agents

Candida albicans. *Candida* species are a group of fungi that are frequently found in humans; *Candida albicans* is the most prevalent form in neonates, followed by *Candida parapsilosis*. *Candida* organisms are oval, yeast-like cells that can bud to reproduce.

Epidemiology. *Candida* bloodstream infections are a major cause of LOS in the newborn, especially in extremely LBW infants. The incidence of candidemia is reported to range from 6.6% to 26% in VLBW infants who are the most fragile and prone to morbidities. Outcomes, such as blindness, severe neurologic impairment, renal failure, and endocarditis, have been reported (Bodin, Godoy, & Phillips, 2015). Early recognition and treatment of fungal infection are imperative to prevent severe CNS complications and death. Prolonged broad-spectrum antibiotic treatment for small premature infants may predispose infants to *Candida* overgrowth in the GI tract. This overgrowth may predispose the infant to disseminated fungemia. Administration of hyperalimentation, frequent use of indwelling venous lines, and invasive procedures may also predispose the infant to *C. albicans* infection. Several studies have implicated previous antibiotic therapy and assisted ventilation as the major factors that correlate with neonatal *Candida* infection. Congenital candidiasis may present at birth and results from a maternal intrauterine infection or exposure to extensive vaginal infection. Chorioamnionitis is associated with intrauterine fetal death and preterm delivery (Bendel, 2016).

Clinical Manifestations and Diagnosis. *Candida* species are responsible for a variety of clinical presentations in the newborn. Mild thrush diaper dermatitis is a common finding in infants who have been on antibiotics. Systemic candidemia can be life-threatening, especially in the extremely premature infant. The newborn infected with disseminated *C. albicans* presents a picture similar to that of any septic infant. Early cultures reported as negative in the clinically ill infant with risk factors for fungal infection should alert the caregiver to the possibility of candidemia. In the NICU, the median age at onset of symptoms is 9 to 10 days. The infant may have respiratory distress, abdominal distention, guaiac-positive stools, carbohydrate intolerance (evidenced by hyperglycemia), candiduria, temperature instability, and hypotension. Infants with congenital candidiasis most likely present with diffuse cutaneous disease, with widespread erythematous maculopapular rash. More severe disease presents with manifestations of systemic viral or bacterial infection (Bendel, 2016).

Mucocutaneous disease can be tentatively diagnosed based on clinical characteristics. It is rarely necessary to obtain cultures of skin or mucous membranes. A potassium hydroxide (KOH) test for budding yeast can be used to distinguish oral thrush from other causes of white coating of the tongue and mucous membranes; KOH is also a rapid screening technique for candiduria (Ericson, Smith, & Benjamin, 2016). A positive *Candida* blood culture should never be considered a contaminated specimen. Intermittently positive cultures may reflect transient candidemia, and, usually, removal of any indwelling catheters and lines and changing of antibiotic therapy may be indicated. Cultures of blood, urine, and spinal fluid should be obtained in fulminant disease. Brain imaging, echocardiogram, renal ultrasound, and dilated retinal examination are warranted for any neonate/infant with candidemia due to the higher risk for dissemination in the preterm population.

Treatment. For mucocutaneous disease, topical agents are indicated. Nystatin is the most commonly used therapy. Oral nystatin should be applied directly to the lesions to improve efficacy. Nystatin ointment or powder is very effective in treating skin lesions, including diaper dermatitis. Some clinicians prescribe oral nystatin when severe diaper dermatitis is present. This regimen is not recommended, however, because the reservoir is usually the lower GI tract. Gentian violet was extensively used in the past and is still prescribed when nystatin is ineffective in the short term. Because of the inconvenience of staining and some local irritation, most clinicians choose systemic therapy when topical treatment is ineffective. The drug of choice for infants with systemic *C. albicans* infection is amphotericin B. This toxic, potent antifungal agent must be used cautiously. The recommended treatment is 1 mg/kg given every 24 hours IV. Therapy should continue for 2 weeks after the first negative blood culture and clearance of clinical signs of the disease. Therapy for CNS involvement should include the addition of 5-fluorouracil (5-FU) as amphotericin B does not cross the blood–brain barrier well. Therapy should be continued at least 3 weeks and until all signs and symptoms of CNS infection have cleared, including negative CSF cultures. Prompt central line removal is advised (AAP, 2018a; Bendel, 2016).

Kidney toxicity is a major side effect of amphotericin B therapy because it causes renal vasoconstriction and decreases both renal blood flow and glomerular filtration rate. This damage can result in hyponatremia, hypokalemia, increased blood urea nitrogen, and increased creatinine, as well as acidosis. If the medication makes the patient oliguric, most providers recommend stopping the drug until the next day. Thrombocytopenia, granulocytopenia, fever, nausea, and vomiting are the common side effects associated with amphotericin B (Bendel, 2016).

Prevention. NICUs with a high incidence of invasive candidiasis are advised to implement a prophylaxis protocol. At this time, antifungal drug prophylaxis is the only regimen shown to be efficacious in randomized controlled trials. Most units use an IV fluconazole prevention protocol. Some use an oral nystatin protocol. A small retrospective descriptive study in one hospital demonstrated that a topical nystatin cream protocol was associated with a very low rate of *Candida* species in extremely LBW infants with central catheters in that NICU (Bodin et al, 2015). More evidence is needed to determine when prophylaxis is needed, what agents are most efficacious, and which agents are considered safe for use in newborn infants of all gestational ages and birthweights.

NOSOCOMIAL INFECTIONS

Both colonization and infection are nosocomial events, meaning "of or related to a hospital." The common meaning of the term *nosocomial* is "hospital acquired." In the neonate, LOS is mostly the result of nosocomial transmission, with the exception of late-onset GBS and HSV infection. Rates of nosocomial infections have declined over the past decade as efforts have been put in place for surveillance and prevention. Risk factors are prematurity, LBW, and extended hospitalization, where many invasive procedures are required. Incidence is indirectly related to birthweight and gestational age, where the highest incidence is found in extremely premature infants. There is considerable variability between nosocomial infection rates among NICUs with reported rates ranging from 10.3% to 31.7% after adjusting for birthweight, gestational age, race, and sex (Ramasethu, 2017). Hospitals in low-to-middle-income countries have higher (3–20 times higher) nosocomial infection rates, mostly due to being poorly equipped to provide aseptic technique for procedures involving sick neonates (Maldonado et al., 2016).

Nosocomial infections are predominantly caused by gram-positive organisms, gram-negative organisms, and yeast. Coagulase-negative staphylococcus has been identified as a major cause of nosocomial infections in the United States since the early 1980s and still remains so. Yeast infections often occur if previous antibiotic therapy has been given. This infection is also associated with colonization of vascular catheters, assisted ventilation, and necrotizing enterocolitis. The most common device-related infections are central line–associated bloodstream infections (CLABSIs), ventilator-associated pneumonia (VAP), urinary catheter-associated urinary tract infections (CAUTI), and ventricular shunt–associated infections (Ramasethu, 2017; Sammons & Coffin, 2016).

Nursery epidemics can be caused by gram-negative and gram-positive or viral organisms because they have (a) the ability to colonize or infect human skin or the GI tract, (b) the ability to be carried from person to person by hand contact, and (c) characteristics that allow existence on hands of personnel or in fluids or on inanimate objects, including IV fluids, respiratory support equipment, solutions used for medications, disinfectants, and banked breast milk.

Resistance to antibiotics is a serious problem in many NICUs, particularly with gram-negative enteric pathogens. Aminoglycoside resistance is a problem in many nurseries, as are colonization and infection with MRSA. Respiratory infections with respiratory syncytial virus (RSV), influenza virus, parainfluenza virus, rhinovirus, and echovirus occur in many nurseries. These are more difficult to identify and thus more difficult to report. CMV infection has been reported as a transfusion-related problem in LBW infants, thus prompting the current policy of using CMV-screened blood donors.

INFECTION CONTROL POLICIES

Policies and procedures in nurseries should be set up by the hospital infection control committee based on the recommendations of the AAP and the CDC. The significance of these policies to newborns should be detailed in a hospital policy book. The following topics should be covered: (a) oclar prophylaxis, (b) skin and cord care, (c) nursery staff ratios, (d) nursery design and environment, (e) handwashing, (f) staff apparel, (g) isolation, (h) visitors, (i) employee health, and (j) epidemic control (Sammons & Coffin, 2016). The simplest, most effective weapon for preventing infection is the liberal use of soap and water!

SUMMARY

Many factors place the neonate at high risk for infection. The nurse is in a unique role to implement methods for prevention of infection in nurseries, to detect early signs and symptoms of infection, and to participate in infection control. A better understanding of the neonatal immune system, methods of perinatal acquisition of organisms, common microorganisms, signs and symptoms of infections, and appropriate therapy provide the nurse with a sound basis for management of care as well as the development and implementation of hospital infection control policies for the NICU. Antibiotic stewardship remains one of the best practices to decrease resistance organisms and, therefore, decrease neonatal morbidity and mortality (McPherson, Liviskie, Zeller, Nelson, & Newland, 2018).

CASE STUDY

Identification of the Problem. Term, female infant admitted to Well Baby Nursery following repeat C-section. Presented with grunting respirations, nasal flaring, and retractions (GFR) by 15 minutes of age.

Assessment: History. Baby S was delivered via repeat C-section under spinal anesthesia to a G2P1001 female with estimated gestational age (EGA) of 39 weeks. Maternal labs: Blood type A+, GBS negative at 35 weeks. RPR nonreactive, Hep B negative, HIV negative, and Rubella immune. Perinatal history: Mother reports a UTI at 36 weeks' gestation, which was treated with Macrodantin. No other problems were noted. Other than this treatment, only prenatal vitamins were taken during pregnancy. Membranes ruptured at delivery with clear amniotic fluid. Apgars: 8 at 1 minute and 9 at 5 minutes. The infant only required drying and stimulation at delivery. She was admitted to the well baby nursery (WBN) at 10 minutes of age for usual newborn care. The neonatal nurse practitioner (NNP) was called to evaluate the infant at 15 minutes of age for GFR. An arterial blood gas (ABG), CBC with diff, and CRP were obtained. The ABG results were: pH 7.223 $Paco_2$ 66 Pao_2 44. CBC and CRP results pending. The infant was transferred to the NICU with blow-by O_2 for further evaluation and treatment.

Physical Examination on Admission to the NICU

- GENERAL: term female infant with marked acrocyanosis. Resting supine with marked grunting, nasal flaring, and subcostal retractions; Spo_2 91% with blow-by O_2 at 5 L/minute
- HEENT: normocephalic, AF soft and slightly concave; bilateral red reflexes and pupils equally reactive to light; ears normally placed; nares patent
- RESP: BBS clear to auscultation; marked GFR; RR 40
- CV: HR regular with normal sinus rhythm; HR 170; no murmur noted; brachial and femoral pulses 2+; capillary refill 4 seconds; BP: 76/35; mean BP: 37
- ABD: abdomen soft and nontender with no hepatosplenomegaly or masses palpable; three-vessel cord
- GI/GU: normal female infant genitalia; patent anus; anal wink present
- NEURO: decreased responses, with eyes open and unblinking; muscle tone markedly decreased
- SKIN: pale pink with mottling; no bruises or "birthmarks" noted
- EXTREMITIES: good passive ROM with 10 fingers and toes each extremity; no hip clunks noted

Differential Diagnoses

- Transient tachypnea of the newborn
- Pneumothorax
- Sepsis
- Pneumonia
- Shock

Diagnostic Tests

Laboratory tests:

- CBC/differential: WBC: 4.7; Hgb: 14.2; Hct: 45.2; Platelet count: 105,000; Segs: 35; Bands: 21; Metas: 2; Myelos: 1
- CRP: 6.8
- Repeat ABG: pH 7.12; $PaCO_2$ 71; PaO_2 49
- Blood cultures X 2. Endotracheal secretion culture. Blood cultures positive at 12 hours for gram-positive cocci; minimal inhibitory concentration (MIC) pending

Imaging tests:

- Chest x-ray: Good expansion with mild reticulogranular appearance; no pneumothorax
- Working diagnosis. GBS sepsis with possible GBS pneumonia (based on preliminary BC report and chest x-ray appearance).
- Development of management plan
- Respiratory support with mechanical ventilation as needed
- Umbilical arterial catheter (UAC) and umbilical venus catheter (UVC) placement for monitoring, sampling, and fluid management
- Continuous monitoring of arterial blood pressure, vital signs, and neurologic status, every 2 to 4 hours
- CBC/diff and CRP every a.m.
- BMP at 12 hours of life and every a.m.
- ABG every 3 to 4 hours as needed for ventilator management
- Maintenance fluid support; fluid boluses to support intravascular volume
- Vasopressors to maintain adequate blood pressure and cerebral blood flow
- Ampicillin and gentamicin IV
- CSF cultures when stable

Implementation and Evaluation of Effectiveness

- Implementation of management plan (immediately after initial assessment in the NICU):
- Infant intubated within the first 30 minutes of life and placed on mechanical ventilation with following settings: SIMV: 40; PIP: 24; Peep: 4; PSV: 12; Fio_2 50% (adjusted to keep Spo_2 90%–97%)
- Chest x-ray to verify endotracheal tube (ETT) placement
- UAC and UVC placed; abdominal x-ray to verify umbilical line placement
- Dopamine 10 mcg/kg/minute initiated by 1 hour of life; weaned to 5 mcg/kg/minute by 36 hours
- Effectiveness of management plan:
- Despite maximum ventilatory support, Baby S developed severe persistent pulmonary hypertension of the newborn (PPHN) and was transferred to a Children's Hospital for possible extracorporeal membrane oxygenation (ECMO) on day 3 of life
- Blood cultures and ETT cultures were positive for group B strep
- CSF cultures were negative
- GBS sepsis and GBS pneumonia were successfully treated with antibiotics

Outcome. The infant did well at the receiving hospital and did not require ECMO. She was treated with iNO for 3 days and was extubated by day 9 of life. Follow-up blood cultures were negative after 14 days of IV antibiotics. She was discharged home at 3 weeks of age and is developmentally appropriate at 3 years of age.

Discussion. Although the incidence of GBS sepsis is decreasing, it still remains the number one cause of EOS in the newborn. In the case presented, a high level of suspicion for sepsis was based on the history of the UTI in the mother. Although a woman's GBS screen is negative at the time it is tested, she may become positive later or the test may reveal a false negative, depending on timing and the technique used. Early recognition and rapid treatment can mean the difference between a poor outcome and a good outcome for the neonate (Committee on Infectious Diseases and Committee on Fetus and Newborn, 2011).

Reference

Committee on Infectious Diseases and Committee on Fetus and Newborn. (2011). Policy statement: Recommendations for the prevention of perinatal group B streptococcal (GBS) disease. *Pediatrics, 128*(3), 1–5. doi:10.1542/peds.2011–1466

EVIDENCE-BASED PRACTICE BOX

One of the most successful evidence-based practice changes in recent history has been the implementation of a group B beta-hemolytic streptococcus (GBS) prophylaxis protocol for the prevention of GBS sepsis in the newborn. During the 1970s, GBS sepsis exceeded *Escherichia coli* as the leading cause of sepsis and meningitis in newborns (Edwards, Nizet, & Baker, 2016). Cases of GBS sepsis continued to increase over the next two decades. In 1996, the Centers for Disease Control and Prevention (CDC) published the first guidelines for the prevention of perinatal group B streptococcal disease, which were based on case reports and clinical trials demonstrating the effectiveness of intrapartum administration of antibiotics to women who were considered at risk for transmitting GBS to their newborns. These guidelines offered two prevention methods: a risk-based approach or a culture-based approach. Although there was a decrease in cases, GBS disease remained a leading cause of neonatal sepsis. Further studies comparing the two strategies revealed data that supported the culture-based method as the most effective strategy in preventing neonatal GBS disease. Therefore, in 2002, the CDC replaced the 1996 guidelines with recommendations that all pregnant women be screened for GBS between 35 and 37 weeks' gestation with the use of intrapartum antibiotic administration during labor for culture-positive women.

Significant declines in the incidence of GBS disease occurred after the implementation of the 1996 guidelines, but a more dramatic decrease occurred after the updated guidelines in 2002. The CDC and other organizations continued to collect data and the guidelines were updated again in 2010. Few changes were made except for information related to testing methods and recommendations for antibiotics for women with penicillin allergy (Verani, McGee, & Schrag, 2010). Since the implementation of intrapartum antibiotic prophylaxis for prevention of neonatal GBS disease, rates of EOS with GBS have declined; however, GBS sepsis continues to be the most common pathogen in term infants and remains the leading cause of disease-related morbidity and mortality among newborns. It is important that we continue to evaluate our practices and make changes that are based on current evidence (Nizet & Klein, 2011).

References

Edwards, M. S., Nizet, V., & Baker, C. J. (2016). Group B streptococcal infections. In C. B. Wilson, V. Nizet, Y. A. Maldonado, J. S. Remington & J. O. Klein (Eds.), *Remington and Klein's infectious diseases of the fetus and newborn infant* (8th ed., pp. 411–456). Philadelphia, PA: Elsevier.

Nizet, V., & Klein, J. O. (2011) Bacterial sepsis and meningitis. In J. S. Remington, J. O. Klein, C. B. Wilson, V. Nizet, & Y. A. Maldonado (Eds.), *Infectious diseases of the fetus and newborn infant* (7th ed., pp. 222–275). Philadelphia, PA: Elsevier.

Verani, J. R., McGee, L., & Schrag, S. J. (2010). Prevention of perinatal group B streptococcal disease: Revised guidelines from CDC, 2010. *MMWR Recommendations and Reports, 59*(RR10), 1–32. Retrieved from https://www.cdc.gov/Mmwr/preview/mmwrhtml/rr5910a1.htm

PARENT VOICES

Deborah A. Discenza

We were about 3 weeks into my daughter's stay in the NICU and had just started doing Kangaroo Care at my request. I was so excited to see how I personally could help my daughter thrive in the NICU environment. Well, one day I walked in, eager to hold her and kangaroo her when the nurse came up to us immediately and said my daughter was not well. Sure enough, we looked into her incubator and she was totally still and very sick. We were told not to touch our daughter nor to stimulate her in any way. They never told us what was wrong and I sat there by her bedside staring at her with a sense of dread. But the nurses said not to touch her, not to comfort her. There was nothing I could do. I felt completely powerless to help my daughter and I had no idea what lay ahead for her. Later we learned it was sepsis and we felt grateful for the care and the antibiotics that helped her through it. The experience left its mark on Becky but also on us, her parents. Things can change in a second.

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ONLINE RESOURCES

Dalal, I., & Roifman, C. M. (2018). Immunity of the newborn. In E. TePas (Ed.), *UpToDate*. Retrieved from https://www.uptodate.com/contents/immunity-of-the-newborn

Tesini, B. L. (n.d.). Neonatal sepsis. *Merck Manual Professional Version* (Online). Retrieved from https://www.Merckmanuals.Com/Professional/Pediatrics/Infections-In-Neonates/Neonatal-Sepsis

Tregoning, J. (n.d.). *Neonatal immunology*. Retrieved From https://www.immunology.org/public-information/bitesized-immunology/immune-development/neonatal-immunology

REFERENCES

Abzug, M. J. (2014). The enteroviruses: Problems in need of treatments. *Journal of Infection, 68*(Suppl. 1), S108–S114. doi:10.1016/j.jinf.2013.09.020

Adams Waldorf, K. M., Gibbs, R. S., & Gravett, M. G. (2016). Obstetric factors associated with infections of the fetus and newborn infant. In C. B. Wilson, V. Nizet, Y. A. Maldonado, J. S. Remington, & J. O. Klein (Eds.), *Remington and Klein's infectious diseases of the fetus and newborn infant* (8th ed., pp. 54–80). Philadelphia, PA: Elsevier.

Allen, U. D., & Robinson, J. L. (2014, April). Prevention and management of neonatal herpes simplex virus infections. *Paediatrics and Child Health, 9*(4), 201–206. doi:10.1093/pch/19.4.201

Anderson-Berry, A. L., Bellig, L. L., & Ohning, B. L. (2015, December 31). Neonatal sepsis. In T. Rosenkrantz (Ed.), *Medscape*. Retrieved from https://emedicine.medscape.com/article/978352-overview

Baley, J. E., & Gonzalez, B. E. (2015). Perinatal viral infections. In R. J. Martin, A. A. Fanaroff, & M. C. Walsh (Eds.), *Fanaroff & Martin's neonatal-perinatal medicine: Diseases of the fetus and newborn* (10th ed., pp. 782–833). Philadelphia, PA: Elsevier.

Basha, S., Surendran, N., & Pichichero, M. (2014). Immune responses in neonates. *Expert Review of Clinical Immunology, 10*(9), 1171–1184. doi:10.1586/1744666X.2014.942288

Basha, S., Surendran, N., & Pichichero, M. (2014). Immune responses in neonates. *Expert Review of Clinical Immunology, 10*(9), 1171–1184. doi:10.1586/1744666X.2014.942288

Bendel, C. M. (2016). Candidiasis. In C. B. Wilson, V. Nizet, Y. A. Maldonado, J. S. Remington, & J. O. Klein (Eds.), *Remington and Klein's infectious diseases of the fetus and newborn infant* (8th ed., pp. 1058–1079). Philadelphia, PA: Elsevier.

Bodin, M. B., Godoy, G., & Phillips, J. B. (2015). Topical nystatin for the prevention of catheter-associated candidiasis in ELBW infants. *Advances in Neonatal Care, 15*(3), 220–224. doi:10.1097/ANC.0000000000000170

Boppana, S. B., Ross, S. A., & Fowler, K. B. (2013). Congenital cytomegalovirus infection: Clinical outcome. *Clinical Infectious Diseases*, *57*(Supp. 4), S178–S181. doi10.1093/cid/cit629

Bradley, J. S., & Nizet, V. (2016). Staphylococcal infections. In C. B. Wilson, V. Nizet, Y. A. Maldonado, J. S. Remington, & J. O. Klein (Eds.), *Remington and Klein's infectious diseases of the fetus and newborn infant* (8th ed., pp. 475–503). Philadelphia, PA: Elsevier.

Britt, W. (2016). Cytomegalovirus. In C. B. Wilson, V. Nizet, Y. A. Maldonado, J. S. Remington, & J. O. Klein (Eds.), *Remington and Klein's infectious diseases of the fetus and newborn infant* (8th ed., pp. 724–781). Philadelphia, PA: Elsevier.

Camacho-Gonzalez, A., Spearman, P. W., & Stoll, B. J. (2013). Neonatal infectious diseases: Evaluation of neonatal sepsis. *Pediatric Clinics of North America, 60*(2), 367–389. doi:10.1016/j.pcl.2012.12.003

Centers for Disease Control and Prevention. (2016). 2016 sexually transmitted diseases surveillance: *Syphilis*. Retrieved from https://www.cdc.gov/std/stats16/syphilis.htm

Centers for Disease Control and Prevention. (2018). Lyme disease. Retrieved from https://www.cdc.gov/lyme/index.html

Cherry, J. D., & Krogstad, P. (2016). Enterovirus, parechovirus, and saffold virus infections. In C. B. Wilson, V. Nizet, Y. A. Maldonado, J. S. Remington, & J. O. Klein (Eds.), *Remington and Klein's infectious diseases of the fetus and newborn infant* (8th ed., pp. 782–827). Philadelphia, PA: Elsevier.

Chu, D., Antony, K., Ma, J., Prince, A., Showalter, L., Moller, M., & Aagaard, K. (2016). The early gut microbiome varies in association with a maternal high-fat diet. *Genome Medicine, 8*(1), 77. doi:10.1186/s13073-016-0330-z

Collins, A., Weitkamp, J.-H., & Wynn, J. L. (2018). Why are preterm newborns at increased risk of infection? *Archives of Disease in Childhood, Fetal and Neonatal Edition, 103*(4): F391–F394. doi:10.1136/archdischild-2017-313595

Darville, T. (2016). *Chlamydia* infections. In C. B. Wilson, V. Nizet, Y. A. Maldonado, J. S. Remington, & J. O. Klein (Eds.), *Remington and Klein's infectious diseases of the fetus and newborn infant* (8th ed., pp. 576–582). Philadelphia, PA: Elsevier.

Edwards, M. S., Nizet, V., & Baker, C. J. (2016). Group B streptococcal infections. In C. B. Wilson, V. Nizet, Y. A. Maldonado, J. S. Remington & J. O. Klein (Eds.), *Remington and Klein's infectious diseases of the fetus and newborn infant* (8th ed., pp. 411–456). Philadelphia, PA: Elsevier.

Embree, J. E. (2016). Gonococcal infections. In C. B. Wilson, V. Nizet, Y. A. Maldonado, J. S. Remington, & J. O. Klein (Eds.), *Remington and Klein's infectious diseases of the fetus and newborn infant* (8th ed., pp. 504–511). Philadelphia, PA: Elsevier.

Eppes, S. C. (2016). Chapter 222: Lyme disease (*Borrelia burgdorferi*). In R. M. Kliegman, B. F. Stanton, J. W. St Geme, & N. F. Schor (Eds.), *Nelson textbook of pediatrics* (20th ed., pp. 1483–1487). Philadelphia, PA: Elsevier.

Ericson, J., Smith, P. B., & Benjamin, D. K. (2016). *Candida*. In R. M. Kliegman, B. F. Stanton, J. W. St Geme, & N. F. Schor (Eds.), *Nelson textbook of pediatrics* (20th ed., pp. 1515–1518). Philadelphia, PA: Elsevier.

Feder, H. M., Jr. (2016). *Borrelia* infections: Lyme disease and relapsing fever. In C. B. Wilson, V. Nizet, Y. A. Maldonado, J. S. Remington, & J. O. Klein (Eds.), *Remington and Klein's infectious diseases of the fetus and newborn infant* (8th ed., pp. 544–557). Philadelphia, PA: Elsevier.

Fleischmann-Struzek, C., Goldfarb, D. M., Schlattman, P., Schlapbach, L. J., Reinhart, K., & Kissoon, N. (2018). The global burden of paediatric and neonatal sepsis: A systematic review. *The Lancet. Respiratory Medicine, 6*(3), 223–230. doi:10.1016/S2213-2600(18)30063-8

Gershon, A. A., Marin, M., & Seward, J. F., (2016). Varicella, measles, and mumps. In C. B. Wilson, V. Nizet, Y. A. Maldonado, J. S. Remington, & J. O. Klein (Eds.), *Remington and Klein's infectious diseases of the fetus and newborn infant* (8th ed., pp. 675–723). Philadelphia, PA: Elsevier.

Gupta, G., Roa, L., Al-Mufti, F., & Roychowdhury, S. (2018). Neonatal meningitis. In A. Kao (Ed.), *Medscape*. Retrieved from https://emedicine.medscape.com/article/1176960-overview

Hong, D. K., & Lewis, D. B. (2016). Developmental immunology and role of host defenses in fetal and neonatal susceptibility to infection. In C. B. Wilson, V. Nizet, Y. A. Maldonado, J. S. Remington & J. O. Klein (Eds.), *Remington and Klein's infectious diseases of the fetus and newborn infant* (8th ed., pp. 81–188). Philadelphia, PA: Saunders.

Jefferies, A. L. (2017). Management of term infants at increased risk for early-onset bacterial sepsis. *Pediatrics & Child Health, 22*(4), 223–228. doi:10.1093/pch/pxx023

Jennewein, M. F., Abu-Raya, B., Jiang, Y., Alter, G., & Marchant, A. (2017). Transfer of maternal immunity and programming of the newborn immune system. *Seminars in Immunopathology, 39*(6), 605–613. doi:10.1007/s00281-017-0653-x

Jensen, M. K., & Balistreri, W. F. (2016). Viral hepatitis. In R. M. Kliegman, B. F. Stanton, J. W. St Geme, & N. F. Schor (Eds.), *Nelson textbook of pediatrics* (20th ed., pp. 1942–1953). Philadelphia, PA: Elsevier.

Karnsakul, W., & Schwarz, K. B. (2016). Hepatitis. In C. B. Wilson, V. Nizet, Y. A. Maldonado, J. S. Remington, & J. O. Klein (Eds.), *Remington and Klein's infectious diseases of the fetus and newborn infant* (8th ed., pp. 828–842). Philadelphia, PA: Elsevier.

Kaufman, D. A., & Manzoni, P. (2015). Perinatal fungal and protozoal infections. In R. J. Martin, A. A. Fanaroff, & M. C. Walsh (Eds.), *Fanaroff & Martin's neonatal-perinatal medicine: Diseases of the fetus and newborn* (10th ed., pp. 751–781). Philadelphia, PA: Elsevier.

Kimberlin, D., & Gutierrez, K. M. (2016). Herpes simplex virus infections. In C. B. Wilson, V. Nizet, Y. A. Maldonado, J. S. Remington, & J. O. Klein (Eds.), *Remington and Klein's infectious diseases of the fetus and newborn infant* (8th ed., pp. 843–865). Philadelphia, PA: Elsevier.

Kimberlin, D. W., Long, S. S., Brady, M. T., & Jackson, M. A. (Eds.). (2018). *Red Book: 2018–2021 report of the committee on infectious diseases*. Elk Grove Village, IL: American Academy of Pediatrics.

Koch, W. C. (2016). Parvoviruses. In R. M. Kliegman, B. F. Stanton, J. W. St Geme, & N. F. Schor (Eds.), *Nelson textbook of pediatrics* (pp. 1568–1572). Philadelphia, PA: Elsevier.

Kollmann, T. R., & Dobson, S. (2016). Syphilis. In C. B. Wilson, V. Nizet, Y. A. Maldonado, J. S. Remington, & J. O. Klein (Eds.), *Remington and Klein's infectious diseases of the fetus and newborn infant* (8th ed., pp. 512–543). Philadelphia, PA: Elsevier.

Kollmann, T. R., Mailman, T. L., & Bortolussi, R. (2016). Listeriosis. In C. B. Wilson, V. Nizet, Y. A. Maldonado, J. S. Remington, & J. O. Klein (Eds.), *Remington and Klein's infectious diseases of the fetus and newborn infant* (8th ed., pp. 457–474). Philadelphia, PA: Elsevier.

K Shetty, A., & Maldonado, Y. (2013). Antiretroviral drugs to prevent mother-to-child transmission of HIV during breastfeeding. *Current HIV research, 11*(2), 102–125.

Lambert, N., Strebel, P., Orenstein, W., Icenogle, J., & Poland, G. A. (2015). Rubella. *The Lancet*, *385*(9984), 2297–2307. doi:10.1016/S0140-6736(14)60539-0

LaRussa, P. S., & Marin, M. (2016). Varicella-Zoster virus. In R. M. Kliegman, B. F. Stanton, J. W. St Geme, & N. F. Schor (Eds.), *Nelson textbook of pediatrics* (20th ed., pp. 1579–1585). Philadelphia, PA: Elsevier.

Leonard, E. C., & Dobbs, K. (2015). Postnatal viral infections. In J. S. Remington, J. O. Klein, C. B. Wilson, V. Nizet, & Y. A. Maldonado (Eds.), *Infectious diseases of the fetus and newborn* (8th ed., pp. 734–750). Philadelphia, PA: Elsevier.

Maldonado, Y. A., Nizet, V., Klein, J. O., Remington, J. S., & Wilson, C. B. (2016). Current concepts of infections of the fetus and newborn infant. In C. B. Wilson, V. Nizet, Y. A. Maldonado, J. S. Remington, & J. O. Klein (Eds.), *Remington and Klein's infectious diseases of the fetus and newborn infant* (8th ed., pp. 3–23). Philadelphia, PA: Elsevier.

Mason WH. (2016). Rubella. In R. M. Kliegman, B. F. Stanton, J. W. St.Geme, & N. F. Schor (Eds.), *Nelson textbook of pediatrics* (20th ed., pp. 1548–1551). Philadelphia, PA: Elsevier.

McAuley, J. B. (2014, September). Congenital toxoplasmosis. *Journal of the Pediatric Infectious Diseases Society*, *3*(Suppl. 1), S30–S35. doi:10.1093/jpids/piu077

McLeod, R., VanTubbergen, C., & Boyer, K. M. (2016). Toxoplasmosis (*Toxoplasma gondii*). In R. M. Kliegman, B. F. Stanton, J. W. St Geme, & N. F. Schor (Eds.), *Nelson textbook of pediatrics* (16th ed., pp. 1723–1232). Philadelphia, PA: Elsevier.

McMillan, J.A., & Maldonado, Y.A. (2015). Less common viral infections. In J. S. Remington, J. O. Klein, C. B. Wilson, V. Nizet, & Y. A. Maldonado (Eds.), *Remington and Klein infectious diseases of the fetus and newborn* (8th ed., pp. 933–948). Philadelphia, PA: Elsevier.

McPherson, C., Liviskie, C., Zeller, B., Nelson, M. P., & Newland, J. G. (2018). Antimicrobial stewardship in neonates: Challenges and opportunities. *Neonatal Network: The Journal of Neonatal Nursing*, *37*(2), 116–123. doi:10.1891/0730-0832.37.2.116

Mendoza-Palomar, N., Balasch-Carulla, M., Gonzalex-Ei Lauro, S., Cespedes, M. C., Andreu, A., Antoinette-Frick, M., . . . Soler-Palacin, P. (2017). *Escherichia coli* early-onset sepsis: Trends over two decades. *European Journal of Pediatrics*, *176*(9), 1227–1234. doi:10.1007/00431-017-2975-z

Modlin, J. F. (2015). Treatment of neonatal enterovirus infections. *Journal of Pediatric Infectious Diseases Society*, *5*(1), 63–63. doi:10.1093/jpids/piv030

Nikonov, O. S., Chernykh, E. S., Garber, M. B., & Nikonova, E. Yu. (2017). Enteroviruses: Classification, diseases they cause, and approaches to/development of antiviral drugs. *Biochemistry* (Moscow), *82*(13), 1615–1631. doi:10.1134/S0006297917130041

Nizet, V., & Klein, J. O. (2016). Bacterial sepsis and meningitis. In C. B. Wilson, V. Nizet, Y. A. Maldonado, J. S. Remington, & J. O. Klein (Eds.), *Remington and Klein's infectious diseases of the fetus and newborn infant* (8th ed., pp. 217–271). Philadelphia, PA: Elsevier.

Peyron, F., Wallon, M., Kieffer, F., & Garweg, J. (2016). Toxoplasmosis. In C. B. Wilson, V. Nizet, Y. A. Maldonado, J. S. Remington, & J. O. Klein (Eds.), *Remington and Klein's infectious diseases of the fetus and newborn infant* (8th ed., pp. 949–1042). Philadelphia, PA: Elsevier.

Ramasethu, J. (2017). Prevention and treatment of neonatal nosocomial infections. *Maternal Health, Perinatology, and Neonatology, 3, 5* doi:10.1186/s40748-017-0043-3

Ranjeva, S. L., Warf, B. C., & Schiff, S. J. (2018). Economic burden of neonatal sepsis in sub-Saharan Africa. *BMJ Global Health, 3*(1), e000347. doi:10.1136/bmjgh-2017-000347

Reef, S. E., & Plotkin, S. A. (2016). Rubella. In C. B. Wilson, V. Nizet, Y. A. Maldonado, J. S. Remington, & J. O. Klein (Eds.), *Remington and Klein's infectious diseases of the fetus and newborn infant* (8th ed., pp. 894–932). Philadelphia, PA: Elsevier.

Sammons, J. S., & Coffin, S. E. (2016). Health Care-associated infections in the nursery. In C. B. Wilson, V. Nizet, Y. A. Maldonado, J. S. Remington, & J. O. Klein (Eds.), *Remington and Klein's infectious diseases of the fetus and newborn infant* (8th ed., pp. 1111–1131). Philadelphia, PA: Elsevier.

Shah, B. A., Padbury, J. F. (2014). Neonatal sepsis: An old problem with new insights. *Virulence*, *5*(1), 170–178. doi:10.4161/viru.26906

Shane, A. L., Sánchez, P. J., & Stoll, B. J. (2017). Neonatal sepsis. *The Lancet*, *390*(10104), 1770–1780. doi:10.1016/S0140-6736(17)31002-4

Shetty, A. K., & Maldonado, Y. (2013). Antiretroviral drugs to prevent mother-to-child transmission of HIV during breastfeeding. *Current HIV Research, 11*(2), 102–125. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/23432487

Simon, A. K., Hollander, G. A., & McMichael, A. (2015). Evolution of the immune system in humans from infancy to old age. *Proceedings of the Royal Society B: Biological Sciences, 282*(1821), 20143085. doi:10.1098/rspb.2014.3085

Simonsen, K. A., Anderson-Berry, A. L., Delair, S. F., & Davies, H. D. (2014). Early-onset neonatal sepsis. *Clinical Microbiology Reviews, 27*(1), 21–47.

Stanberry, L. R. (2006). Neonatal herpes in premature infants: A special problem. *Pediatrics, 118*(6), 2543–2544.

Swanson, E. C., & Schleiss, M. R. (2013). Congenital cytomegalovirus infection: New prospects for prevention and therapy. *Pediatric Clinics of North America, 60*(2), 335–349. doi:10.1016/j.pcl.2012.12.008.

Verani, J. R., McGee, L., & Schrag, S. J. (2010). Prevention of perinatal group B streptococcal disease: Revised guidelines from CDC, 2010. *MMWR Recommendations and Reports, 59* (No. RR-10), 1–32. Retrieved from https://www.cdc.gov/Mmwr/preview/mmwrhtml/rr5910a1.htm

Weinberg, G. A., D Angio, C. T. (2016). Laboratory aids for diagnosis of neonatal sepsis. In C. B. Wilson, V. Nizet, Y. A. Maldonado, J. S. Remington, & J. O. Klein (eds). *Remington and Klein's infectious diseases of the fetus and newborn infant* (8th ed., pp. 1132–1146). Philadelphia, PA: Elsevier.

Zaidi, A. K. M., Darmstadt, G. L., & Stoll. B. J. (2016). Neonatal infections: A global perspective. In C. B. Wilson, V. Nizet, Y. A. Maldonado, J. S. Remington, & J. O. Klein (Eds.). *Remington and Klein's infectious diseases of the fetus and newborn infant* (8th ed., pp. 24–53). Philadelphia, PA: Elsevier.

CHAPTER 12

Integumentary System

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INTRODUCTION

Skin phenomena, along with other examination findings, are used to assess the maturity, duration of pregnancy, and neonatal vitality. The skin of a preterm infant makes up 13% of the body weight, compared with 3% in adults. This large organ provides a barrier against infection, protects internal organs, assists in acid mantle development, contributes to temperature regulation and prevention of insensible water loss (ISWL), stores fats, excretes electrolytes and water, and provides tactile sensory input. The sensations of touch, pressure, temperature, pain, and itch are received by millions of microscopic dermal nerve endings. The skin is instrumental in early establishment of the mother–infant relationship in that the quality of touch and stimulation that an infant receives is responsible for the infant's later responses to other people and to the environment. Thus, the skin fulfills a task of vital importance, particularly in the area of maternal–child nursing.

Care practices that affect the fragile, underdeveloped skin of the premature infant present major concerns as well as dilemmas for care providers. Life support and monitoring equipment must be securely attached and frequently removed or replaced; this practice can cause trauma to the skin. Necessary invasive procedures, such as vascular access, blood sampling, and chest tube insertion, invade the skin's barrier. Trauma to skin can result in the diversion of an excessive proportion of caloric intake to tissue repair. Other effects of trauma to premature skin include the energy demands of electrolyte imbalances and increased evaporative heat loss through damaged or immature skin and the risk of toxicity when substances are applied to the skin surface.

Trauma to the skin creates portals of entry for bacteria and fungus in an already immune-compromised host. Significant morbidity and mortality can be attributed to practices that cause either trauma to skin or alterations in normal skin function. Iatrogenically -caused skin problems—including burns and caustic lesions from isopropyl alcohol and erythema and skin craters from transcutaneous oxygen monitoring—have been reported. Increased skin permeability and percutaneous toxicity from drugs and chemicals have also been documented in neonates.

This chapter covers the development and structure of skin, the normal physiological variations in newborn skin, and dermatologic diseases. This information is then incorporated into the management of neonatal skin.

SKIN STRUCTURE AND FUNCTION

Skin consists of three anatomically distinct layers: the epidermis, the dermis, and the subcutaneous tissue. The uppermost layer of the epidermis is the *stratum corneum*, primarily composed of nonliving cells made of protein with layers of lipids that bind them; this has been described as similar to the "bricks and mortar of a wall." These cells, once exfoliated in utero, form part of the *vernix caseosa*, the cheese-like substance that covers and protects fetal skin. The bottom, living basal layer contain keratinocytes, which constantly replace the keratin cells in the *stratum corneum*; it takes approximately 26 days for keratinocytes to migrate up to the *stratum corneum*. Approximately 20% of an adult's protein requirement is needed for this purpose. Keratin-forming cells—which cornify the outer layer of the epidermis—and melanocytes are contained in the lower levels of the epidermis. Melanocytes begin producing melanin, or pigment, before birth and distribute it to the epidermal cells. Active pigmentary activity can be observed before birth in the epidermis of infants of dark-skinned races but little evidence of such activity exists in white fetuses (Moore & Persaud, 2015).

The dermis lies directly under the epidermis and is 2 to 4 mm thick at birth. It is a closely woven layer of collagen, a fibrous protein, and elastin fibers. This fibrous complex provides mechanical strength as well as elasticity and allows the skin to withstand frictional stress while extending easily over joints. At term, the dermis is well organized but is thinner and has higher water content compared to the adult dermis (Loomis, Koss, & Chu, 2008). Many nerves and a rich supply of blood vessels are contained there. They nourish the skin cells and act as carriers of the sensations of heat, touch, pressure, and pain from the skin to the brain.

Hair originates from deep in the dermis. Down-growths, called epidermal ridges, which extend into the developing dermis, result from a proliferation of cells in the basal layer. These ridges are permanently established by 17 weeks' gestation and produce ridges and grooves on the surface of the palms, including the fingers, and on the soles of the feet, including the toes.

Determined genetically, this type of pattern constitutes the basis for the use of fingerprints in criminal investigations and medical genetics. Dermatoglyphics is the study of the pattern of these epidermal ridges. The presence of abnormal chromosome complements affects the development of the ridge patterns. For example,

infants with Down syndrome exhibit distinctive hand and feet patterns that are of diagnostic value (Moore & Persaud, 2015).

The major component of the subcutaneous layer is fatty connective tissue. The subcutaneous fat functions as a heat insulator, a shock absorber, and a calorie reserve area. Fat accumulation occurs predominantly in the last trimester. Sebaceous glands are found in both the dermis and the subcutaneous layer. Well-developed and potentially functional at birth, these glands have only minimal function until puberty. Sweat glands are also found in the dermis and the subcutaneous layer and are affected directly by external environmental temperature. In premature infants, sweat gland maturation occurs between 21 and 33 days of age. In term infants, this maturation occurs at about 5 days of age. Poor sweat production in the premature infant is caused by sweat gland immaturity. However, adult function is not achieved until the second or third year of life.

Term infant skin is soft, wrinkled, velvety, and covered with *vernix caseosa* (Visscher et al., 2005). Transformation of the fetal circulation is evident soon after the cord is cut, as the skin develops the intense red coloration characteristic of the newborn. This color may remain for hours. A blue, blotchy appearance may occur if the infant is exposed to a cool environment.

The insulating layer of vernix is usually lost during the first few days of life through traditional newborn skin care (Dyer, 2013). This results in a loss of insulation for the *stratum corneum*, which then peels off, thus resulting in skin with a grayish-white or yellowish hue. Visible desquamation of newborn skin comes to an end after about 7 days. The vernix protects the fetus from maceration by the amniotic fluid, facilitates the development of the *stratum corneum*, assists in the development of the acid mantle, provides bactericidal protection, and contributes to the development of epidermal barrier function (Visscher, Adam, Brink, & Odio, 2015).

In comparison with the skin of the term infant, the premature infant's skin is more transparent, gelatinous, and unwrinkled. Lanugo, which has been lost in the full-term infant, may be present in varying degrees and is one criterion used to estimate gestational age. Additionally, subcutaneous edema may be present and is clinical evidence of a cutaneous excess of water and sodium. This edema decreases within the first few days of life and the skin then lies loosely over the infant's entire body. The immaturity of the infant's skin is linked to the premature newborn's difficulty maintaining body temperature. A poorly developed fat supply and a large body surface area in relation to body weight add to temperature instability.

The premature infant has been shown to have a less well-developed *stratum corneum*; at less than 30 weeks' gestation there may be only two to three layers of *stratum corneum*. This immaturity results in the premature infant's decreased capacity to resist particles, viruses, parasites, and bacteria in the external environment, leaving the infant readily susceptible to infection and irritation of the skin (Lawton, 2013).

Transferring from the intrauterine aquatic environment to the external atmospheric environment stimulates and accelerates the maturation of skin functions. Embryologic skin development is described in Exhibit 12.1.

Developmental Variations

Several factors are responsible for the functional differences between premature and term infants' skins. These differences subside with increasing gestational and postnatal ages (Table 12.1).

EXHIBIT 12.1

Embryologic Development of Skin

The skin consists of two morphologically different layers derived from two different germ layers. The epithelial structures (epidermis, pilosebaceous-apocrine unit, eccrine unit, and nails) are ectodermal derivatives. The ectoderm also gives rise to the hair, the teeth, and the sense organs of smell, taste, hearing, vision, and touch—everything involved with events that occur outside the organism. Mesenchymal structures (collagen, reticular, and elastic fibers; blood vessels; muscles; and fat) originate from the mesoderm. These developments are outlined in Table 12.2.

The epidermis, which develops from the surface ectoderm, consists of one layer of undifferentiated cells in a 3-week-old embryo. By 4 weeks' gestational age, it has an inner germinative layer of cuboidal cells with dark, compact nuclei and an outer layer of slightly flatter cells covered by microvilli. By about the middle of the second month of gestation, some of the cells begin to be crowded to the surface and form a thin, protective layer of flattened cells known as the periderm. The cells of this layer continually undergo keratinization and desquamation and are replaced by cells arising from the basal layer. The periderm is often called the epitrichial ("upon the hair") layer of the epidermis because the hairs that later grow up from the deeper layers are said not to penetrate this thin surface layer but to push it up on their growing tips, thus causing it to be cast off if it has not already disappeared. These exfoliated cells form part of the *vernix caseosa*.

During the latter part of the second month, the epithelium tends to become thicker. This occurs (at first) by a staggering of the nuclei and the beginning of cell rearrangement, which leads rapidly to the formation of an intermediate layer between the flattened cells of the epitrichial layer and the basal layer adjacent to the underlying dermis. The cells of this intermediate layer tend to become enlarged and show a high degree of vacuolation. The basal layer of the epidermis is later called the stratum germinativum (Moore & Persaud, 2015).

At the end of the second month of gestation, the cutaneous nerves, detectable in the embryonic dermis by about the fifth week of gestation, appear to be functional, although the skin is primitive by comparison with that of an adult.

At about 10 weeks' gestation, fingernail development begins at the tips of the digits. A thickened area of epithelium on the dorsum of each digit is the first sign of nail formation. Our nails are adaptations of the epidermis, homologous to the claws and hooves of lower mammals, and are formed by a modified process of keratinization. Development of the fingernails is begun and completed (30–34 weeks) before that of the toenails (35–38 weeks).

By about 11 weeks' gestation, collagen and elastic connective tissue fibers begin to develop in the dermis. The epidermal-dermal junction, which has been smooth up to this time, now becomes wavy as epidermal thickenings grow down into the dermis of the palm and the soles of the feet. Dermal papillae develop in

(*continued*)

EXHIBIT 12.1 (*continued*)

these dermal projections. Capillary loops develop in some dermal papillae and Meissner's corpuscles, which are the sensory nerve endings of touch, form in others (Moore & Persaud, 2015). These epidermal ridges produce ridges and grooves in a genetically determined pattern and are the basis for fingerprinting and footprinting. The development of these ridges can be distinctly affected by the presence of abnormal chromosome complements (e.g., as occurs in Down syndrome). These ridges are permanently established by about 17 weeks of gestation.

During the third to fourth month of gestation, the *stratum germinativum* differentiates from the rest of the epithelium. These cells are termed the germinative layer because they undergo the repeated cell divisions that are responsible for the growth of the epidermis.

During the fourth month of gestation, the epithelium starts to become many cells thick and keratin begins to accumulate in the cells above the stratum germinativum layer. Daughter cells from the basal layer are crowded upward and undergo progressive changes in each layer and finalize in cornification. The thin stratum *granulosum epidermidis*, which contains keratohyalin granules, is the layer directly above the stratum germinativum. The next higher layer is the thin and clear stratum *lucidum epidermidis*, the content of which is a fluid—eleidin—that replaces the granules. Above that is the keratinized multilayered stratum *corneum epidermidis* (Moore & Persaud, 2015). As the keratin accumulates in these cells, they become more and more sluggish and finally die, so that the surface layer of the epidermis is made up of tough, scale-like, dead cells that form a relatively impermeable membrane.

In areas such as the soles of the feet and the palms of the hands, where the skin is subjected to more than ordinary wear, the keratinization of the outer layer is much heavier than in the general body surface. Of interest, however, is that the greater thickness of palmar and plantar epidermis becomes evident in the embryo long before it is possible for these areas to have been subjected to any more wear than other parts of the skin. When the aforementioned layers are all completely differentiated, the structure of fetal epidermis resembles that of adult epidermis.

During the early fetal period, neural crest cells migrate into the dermis and differentiate into melanoblasts. At about 17 to 20 weeks of gestation, these melanoblasts differentiate into melanocytes, migrate to the epidermal–dermal border, and begin to produce melanin. Fetal melanocytes in white races contain little or no pigment, whereas in dark-skinned races, they produce melanin granules. The skin of black newborns is only a little darker than that of white newborns. The skin at the bases of the fingernails and toenails is often noticeably darker, however.

The skin of black infants continues to darken after birth as increased melanin production occurs in response to light. When melanocytes remain behind in the dermis, they appear bluish through the overlying cutaneous tissue and are called mongolian spots. Some believe that it is not the number of melanocytes present that is important but rather their activity level. The hormone secreted by the pituitary gland that controls the clumping or dispersion of the melanin granules is a melanocyte-stimulating hormone.

At around 20 weeks' gestation, the eyebrows, upper lip, and chin hair are first recognizable. On the general body surface, the hair makes its appearance about a month later. These fine hairs are called lanugo. The emergence of this hair breaks off the periderm and the periderm becomes one component of the *vernix caseosa*. The other components of vernix are sebum from the sebaceous glands, fetal hair, and desquamated cells from the amnion (Moore & Persaud, 2015). The vernix protects the epidermis against a macerating influence that would be exerted by the amniotic fluid and acts as a lubricant to prevent chafing injuries from the amnion as the growing fetus becomes progressively confined in its fluid-filled sac.

Between 21 and 24 weeks' gestation, the fetus's skin is wrinkled, translucent, and pinkish-red because blood in the capillaries has become visible. Head and lanugo hair are well developed in a 26- to 29-week fetus. At this same time, eccrine sweat glands are anatomically developed and are found over the entire body. Their function, however, is somewhat immature in the perinatal period.

Brown adipose tissue cells begin to differentiate in the seventh month of gestation, and the accumulation of subcutaneous fat begins to smooth out the many skin wrinkles. Between the 30th and 34th week of gestation, the skin is pink and smooth and the lanugo is beginning to shed. The fingernails reach the fingertips but the distal part of the nail is still thin and soft (Moore & Persaud, 2015). During the last trimester of pregnancy, subcutaneous fat accumulates and the fetus acquires a plump appearance. The composition of amniotic fluid tested at this time reflects skin function. The number of anucleated cells and keratinized lipid-containing skin flakes increases.

Thickness of the *Stratum Corneum* and Permeability

The *stratum corneum* layer provides the barrier properties of the skin. This barrier is composed of keratinocytes coated by intercellular lipids. The *stratum corneum* begins to develop in the fetus after 21 weeks estimated gestational age (EGA). The *stratum corneum* in infants of 28 weeks' gestation consists of only a few cell layers and is markedly thinner than that of term infants. These findings correlate with the immaturity of barrier function of the *stratum corneum* and are characterized by increased permeability and increased transepidermal water loss (TEWL; Bhatia, 2006). By 34 to 35 weeks EGA, the *stratum corneum* has developed sufficiently to offer some protection (Visscher et al., 2015).

The full-term infant has a fully functional *stratum corneum*. The *stratum corneum*, the nonliving layer of the epidermis, contains 10 to 20 layers in adults and term infants. The *stratum corneum* of term newborns has been shown to have lower TEWL and hydration (SCH) than that of adult skin, with the lowest levels seen on the first day of life. This suggests that the barrier is relatively impermeable to water to protect from maceration in utero and that a gradual drying process occurs over the first few days of life. In addition, the TEWL in different areas—such as the forehead, palms, and soles—is lower in newborns, whereas levels are higher on the forearm region (Yosipovitch, Maayan-Metzger, Merlob, & Sirota, 2000).

Despite reports of normal barrier function at birth, studies indicate that infant skin is prone to higher percutaneous absorption

TABLE 12.1

STRUCTURAL DIFFERENCES BETWEEN INFANT AND ADULT SKIN

	Premature	Full Term	Adult
Epidermis	Thinner cells compressed	*Stratum corneum* appears as adherent cell layers	Good resistance to penetration
	Fewer desmosomes	Melanin production low	
	Fewer layers of *stratum corneum*		
	Melanin production low		
Dermoepidermal junction	Fewer hemidesmosomes		
	Less cohesion between layers		
Dermis	Fewer elastin fibers	Fewer elastin fibers	Full complement of elastin fibers
	Thinner than in the adult	Thinner than in the adult	
Eccrine glands	May be more typical of fetus than adult	Equivalent in structure to adult	Distribution less dense than in infant
	Ducts patent	Denser distribution	
	Secretory cells undifferentiated		
Hair	Lanugo hair may be present	Vellus hair characteristic	Both vellus and terminal hairs
	Hair growth synchronous	Hair growth synchronous	Hair growth dyssynchronous
Sebaceous glands	Large and active	Large and active but diminishing rapidly in both size and activity for several weeks after birth	Large and active
Nerve and vascular system	Not fully organized	Vascular system not fully organized until 3 months	Adult pattern
	Most nerves are small in diameter, unmyelinated, sensory, and autonomic	Cutaneous nerve network not fully developed; may continue to develop until puberty	
	Unmyelinated nerves are typically fetal in structure	Most nerves are small in diameter, unmyelinated, sensory, and autonomic	
	Meissner's touch receptors not fully formed	Meissner's touch receptors not fully formed	
		Good resistance to penetration	
Permeability	Highly permeable	Good resistance to penetration	
	Higher penetrability of fat-soluble substances	Higher penetrability of fat-soluble substances	
	Greater absorption because of higher skin surface: body weight ratio	Greater absorption because of higher skin surface: body weight ratio	

(*continued*)

TABLE 12.1

STRUCTURAL DIFFERENCES BETWEEN INFANT AND ADULT SKIN (*continued*)

	Premature	Full Term	Adult
Eccrine sweating	Reduced sweating capability, especially for first 13–24 days	Reduced sweating capability, especially for first 2–5 days	Full sweating capability
Photosensitivity	Melanin production low; will sunburn readily	Melanin production low; will sunburn readily	Sensitivity to sun depends on skin type
Related conditions	Reduced ability to ward off infection because of deficient immune system	Reduced ability to ward off infection	Readily sensitized to allergens
	Low reactivity to allergens	Low reactivity to allergens	

Source: Adapted from Shalita, A. (1981). *Principles of infant skin care.* Skillman, NJ: Johnson & Johnson Baby Products.

TABLE 12.2

EMBRYONIC AND FETAL DEVELOPMENT OF SKIN

Weeks of Gestation	Development
3	Epidermis, which develops from surface ectoderm, consists of one layer of cells.
5	Cutaneous nerves are detectable in embryonic dermis.
6–7	Periderm, a thin, protective layer of flattened cells, is formed.
11	Collagen and elastic fibers are developing in the dermis. Epidermal ridges (fingerprints) are forming. Nails begin to develop at the tips of the digits.
13–16	Scalp hair patterning is determined.
17–20	Melanocytes migrate to the epidermal-dermal junction and begin to produce melanin. Skin is covered with *vernix caseosa* and lanugo. Keratin is accumulating in the epidermis.
21–25	Skin is wrinkled, translucent, and pink to red because blood in the capillaries has become visible.
26–29	Subcutaneous fat begins to be deposited and starts to smooth out the many wrinkles in the skin. Eccrine sweat glands are anatomically developed and found over the entire body; their function, however, is somewhat immature in the perinatal period.
30–34	Skin is pink and smooth. Fingernails reach fingertips. Lanugo begins to shed.
35–38	Fetuses are usually plump. Skin is usually white or bluish-pink. Toenails reach toe tips.

Embryonic period: undoubtedly the most important period of human development because the beginnings of all major external and internal structures develop. Fetal period (ninth week to birth): primarily concerned with growth and differentiation of tissue and organs that started to develop during the embryonic period.

Source: Adapted from Ackerman, A. (1985). Structure and function of the skin. In S. Moschella & H. Hurley (Eds.), *Dermatology* (2nd ed., Vol. 2). Philadelphia, PA: Saunders.

and exhibits a greater tendency to irritant and allergic contact dermatitis, prompting some to say that barrier function is not fully developed at birth (Hoeger & Enzmann, 2002). In addition, infant *stratum corneum* is 30% thinner than adult, with the overall epidermis 20% to 30% smaller. Keratinocyte cells are smaller; with higher cell turnover rate that may explain observations of faster wound healing in infant skin (Stamatas, Nikolovski, Mack, & Kollias, 2011).

The *stratum corneum* of premature infants was once thought to rapidly mature and reach adult barrier function within approximately 2 weeks after birth. However, this has been shown to be a slower process in premature infants less than 27 weeks' gestation; rates of TEWL are nearly double adult levels, even at 28 days of life (Hammarlund & Sedin, 1979). In infants of 23 to 25 weeks' gestation, skin barrier function reaches mature levels much more slowly (Agren, Sjors, & Sedin, 1998), as long as 8 weeks after birth in a 23-week gestation infant (Kalia, Nonato, Lund, & Guy, 1998). The undeveloped *stratum corneum* of the premature infant's skin results in increased TEWL and evaporative heat loss and contributes to the difficulty the premature newborn experiences in maintaining fluid balance and body temperature.

Neonatal skin is 40% to 60% thinner than adult skin and the body surface/weight ratio is nearly five times greater, placing the newborn at risk for toxicity from topically applied substances (Mancini, 2004; Siegfried, 2008). The skin of a premature infant is remarkably permeable; permeability correlates inversely with gestational age. Sekkat, Kalia, and Guy (2004) have developed an in vitro model to examine the biophysical characteristics of TEWL in premature infants. This model will help clinicians understand how procedures coupled with gestational age can affect skin integrity, permeability, and TEWL.

Toxicity due to topically applied substances secondary to the increased permeability of both preterm and term infants' skin has been reported in numerous cases (Siegfried, 2008). All topical solutions during the first month of life should be carefully evaluated in relation to potential benefits, risks, and effectiveness.

Dermal Instability

Collagen in the dermis increases with gestational age as the tendency toward water fixation and edema decreases. The other component of the dermis, the elastin fibers, is formed mostly after birth and may not become fully mature until 3 years of age. **Quality and Safety: Protection from pressure and ischemic injury includes routine turning and repositioning on surfaces such as gelled pads or water mattresses** (Association of Women's Health, Obstetric, and Neonatal Nurses [AWHONN], 2018).

Diminished Cohesion

Another variation in the premature infant's skin structure and function is the diminished cohesion between the dermis and the epidermis. The junction of the epidermis and the dermis, normally connected by numerous fibrils, has fewer and more widely spaced fibrils in the premature infant than in term infants or adults. These fibrils become stronger with increasing gestational and postnatal age (Holbrook, 1982). Because care of the premature infant in the NICU often requires intravenous lines, cardiorespiratory electrodes, endotracheal tubes, and umbilical artery catheters, the premature infant is at higher risk of blistering and stripping of the epidermis when adhesives used to secure these devices and monitors are removed (Cousins, 2014). **Emergency Alert: The cohesion between many of the currently used adhesives and the *stratum corneum* may be stronger than the bond between the dermis and the epidermis.**

Skin pH

Another developmental variation of infant skin resides in the functional capacity of the skin to form a surface pH of less than 5.0, which is the acid mantle. A skin surface pH of less than 5.0 is ordinarily seen in both children and adults.

Full-term newborns' skin was found to have a mean pH of 6.34 immediately after birth. Within 4 days, the pH decreased to a mean of 4.95, and between 7 and 30 days it further decreased to 4.7. In a later study of 127 low-birth-weight infants, these authors documented that the mean pH decreased from 6.7 (day 1) to 5.04 (day 9). However, a different technique for measuring pH was used than in the previous study; thus, the absolute values for pH may not be comparable. They concluded that acidification of the skin is independent of gestational age (C. Fox, Nelson, & Wareham, 1998).

An acidic skin surface is credited with having bactericidal qualities against some pathogens and serves in the defense against microorganisms. This acid mantle contributes to the *stratum corneum*'s innate immune function by inhibiting the growth of pathogenic bacteria (Larson & Dinulos, 2005; Visscher et al., 2011). The retention of *vernix caseosa* has been shown to assist in earlier acidification of the newborn skin and may help to facilitate colonization by normal flora after birth (Tollin et al., 2005), while an increased pH may reduce *stratum corneum* integrity and enhance susceptibility to mechanical damage (Visscher et al., 2011).

Melanin Production

One of the primary functions of melanin is to screen the skin from the sun's harmful rays by absorbing their radiant energy. Although melanin production—and therefore pigmentation—are lower during the neonatal period than later in life, certain areas—such as the linea alba, the areola, and the scrotum—are often deeply pigmented as a result of high circulating levels of maternal and placental hormones. Melanin production in premature infants is even less than in term infants, thus placing them at greater risk for damage from sunlight and ultraviolet light (Williams, 2008).

Assessment and Physiologic Variations

Acrocyanosis, or peripheral cyanosis involving the hands, feet, and circumoral area, is a common finding in the newborn. It occurs because of sluggish blood flow in the feet and hands that results from limited development of the peripheral capillary circulation. Acrocyanosis usually resolves within the first few days of life but may reappear with cold stress (Lucky, 2015). It occurs more often in premature infants.

Pallor is most commonly a sign of anemia, hypoxia, or poor peripheral perfusion that results from hypotension or infection. Meconium staining is caused by the passage of meconium in utero and usually requires at least 6 hours of meconium contact to stain the skin.

Jaundice, which occurs in 50% to 70% of newborns, is a yellowing of the skin and develops because of the presence of indirect bilirubin in the blood formed from the body's normal breakdown of red blood cells. Bilirubin is normally processed by the liver and is eliminated in the urine and feces. In newborns, the body cannot eliminate bilirubin as fast as it is produced.

For visible staining of the skin and sclera, a bilirubin level of at least 5 mg/100 mL is required. The predictable head-to-toe progression of jaundice over the body gives a crude estimate of the level of bilirubin. Typically, the bilirubin level is highest at 3 to 5 days (Bromiker, Bin-Nun, Schimmel, Hammerman, & Kaplan, 2012).

Risk factors for high bilirubin levels or kernicterus, a neurologically damaging condition caused by hyperbilirubinemia, are: bruising at birth, prematurity, breastfeeding and poor feeding,

glucose-6-phosphate dehydrogenase deficiency (G6PD), East Asian or Mediterranean descent, jaundice prior to 24 hours, and a prior sibling with jaundice. Jaundice fades after the bilirubin level returns to normal. *Linea nigra* is a line of increased pigmentation from the umbilicus to the genitals. This area of benign pigmentation may become less noticeable as the infant's skin darkens. Mongolian spots are collections of melanocytes located in the dermis that are most frequently seen at birth. They are slate blue, gray, or black, shaped as irregular, bruise-like spots that are seen primarily over the sacrum and the buttocks but may extend over the back and shoulders. Most commonly seen in newborns with darkly pigmented skin, they are found in 96% of African American, 86% of Asian, and 13% of Caucasian infants (Lucky, 2008). Although they look like bruises, they are harmless and resolve over several years.

Lanugo is the fine downy hair that is most commonly seen over the back, shoulders, and facial areas of a premature newborn. It is shed at the seventh to eighth month of gestation and is one criterion used to estimate gestational age.

Milia are common papules that occur primarily on the face but may also occur in other locations. They are seen as small, white, pinhead-sized bumps scattered over the chins, cheeks, noses, and foreheads of 25% to 40% of full-term babies (Dinulos & Darmstadt, 2005). They spontaneously resolve within the first month of life. Mothers should be instructed not to squeeze or prick these pimple-like spots. Milia can develop on the foreskins of infant boys; these are called epidermal inclusion cysts. When they occur on the palate, they are called Epstein's pearls.

Miliaria (prickly heat) is a general term for describing obstructions of the eccrine duct. The cause is retention of sweat as a result of edema of the *stratum corneum*; this edema blocks eccrine pores, thus resulting in four types of miliaria: rubra, crystallina, pustulosa, and profunda. Most common locations are the forehead and upper trunk (Howard & Frieden, 2015).

Miliaria pustulosa and *miliaria profunda* are rarely seen in temperate climates. *Miliaria rubra* is commonly observed in infants exposed to excessive environmental temperatures with humidity. It appears as pink or white pimples with a little redness around them. They resolve when the infant is moved to cooler temperatures. *Miliaria crystallina* presents as clear, 1- to 2-mm superficial water blisters without inflammation. The distribution and grouping of vesicles that contain no eosinophils help to differentiate them from *erythema toxicum neonatorum*.

Harlequin color change is a dramatic but benign phenomenon in which the color on the dependent half of an infant in a side-lying position turns deep red while the upper half is pale. The face and genitalia may be spared and the color reverses when the infant is turned. Attributed to a temporary imbalance in the autonomic regulatory mechanism of the cutaneous vessels, this phenomenon is more common in low-birth-weight infants—whether well or sick—but can affect up to 10% of full-term babies (Lucky, 2015).

Vernix caseosa is a grayish-white cheesy substance that is a mixture of 80% water, protein, lipids, and desquamating cells (Visscher et al., 2015). This covering is protective to the fetal skin while the fetus is in utero and helps the infant slide through the birth canal. Vernix production begins at the end of the second trimester and accumulates in a cephalocaudal manner (Haubrich, 2003). The vernix covering diminishes as pulmonary surfactant rises and the fetus reaches term (Moraille, Pickens, Visscher, & Hoath, 2005). Surface distribution is dependent on gestational age, type of delivery, birth weight, race, gender, and the presence of meconium. The World Health Organization (WHO; 2015) recommends leaving residual vernix in place, after initial drying, to wear off with normal care and handling for at least 6 hours before bathing. **Quality and Safety:** *The AWHONN Neonatal Skin Care Evidence-Based Practice Guideline*, Fourth Edition, **recommends leaving vernix on the skin and delaying the first bath until between 6 and 24 hours of age** (AWHONN, 2018). In clinical care, vernix has been thought of as an unwanted soil from intrauterine life but recent research has revealed that vernix has many functions and potential benefits for the newborn. These functions and potential benefits include: protection against infection (Tollin et al., 2005), decreased skin permeability and TEWL (Visscher & Narendran, 2014; Yoshio, Lagercrantz, Gudmundsson, & Agerberth, 2004), skin cleansing (Moraille et al., 2005), moisturization of the skin surface (Visscher & Narendran, 2014), development of the epidermal barrier (Tansirikongkol, Visscher, & Wickett, 2007), pH development (Colwell, 2015), and temperature regulation.

Cutis marmorata, or mottling, is a normal physiological vascular response to cool air. This generalized mottling reflects the infant's vasomotor instability. The marbling disappears with rewarming and is uncommon after several months of age. Mottling is often prominent in infants with Cornelia de Lange syndrome and Down syndrome (Trisomy 21).

TERMINOLOGY

Ecchymoses appear as black and blue bruises of varying sizes anywhere on the body. Primarily seen over the presenting part in a difficult vertex delivery or a vaginal breech delivery, ecchymosis is most frequently due to trauma associated with labor and delivery. It occurs more commonly in the fragile premature infant. This bruising, however, can be indicative of serious infection or bleeding disorders. Large areas of bruising may require phototherapy as a result of hyperbilirubinemia (Jensen & Galbraith, 2015).

Petechiae are pinpoint hemorrhagic areas, less than 1 mm in diameter, scattered over the upper trunk and face as a result of pressure during the descent and rotation of birth. Their incidence is increased when the umbilical cord has been around the neck or when the cervix clamps down after delivery of the head. They do not disappear with blanching because the blood is contained in the tissues. They usually fade within 24 to 48 hours. If they continue to develop or are unusually numerous, a complete workup for infection or bleeding disorders should be performed.

Thrombocytopenia should be suspected when the infant presents with general cutaneous petechiae. It frequently accompanies neonatal infections and is most commonly associated with the TORCH diseases (toxoplasmosis, others, rubella, cytomegalovirus [CMV], and herpes simplex).

Macules are nonpalpable, nonraised lesions less than 1 cm in diameter identified only by color change. They are seen in measles, rubella, scarlet fever, roseola, typhoid fever, and drug reactions.

Papules are superficial elevated solid lesions less than 1 cm in diameter. They are firm and not fluid-filled. They may follow the macular stage in many eruptive diseases. Vesicles are skin elevations that contain serous fluid (blisters). They are commonly seen with herpes simplex, insect bites, and poison ivy.

Pustules are localized accumulations of pus in, or just beneath, the epidermis. They are often centered around appendageal structures (e.g., hair follicles) and are usually caused by bacterial infections or skin abscesses. When a pustule breaks, the degree of crusting is more marked than occurs with the rupture of a vesicle.

Nodules are deep solid lesions larger than 1 cm in diameter. Nodules are similar to papules but are larger. Because of their size, they are more likely to have a dermal component than are papules.

Lesions Related to the Birth Process

Caput succedaneum is a diffuse, generalized edema of the presenting part of the scalp. It is the result of venous congestion caused by the pressure of the uterus, cervix, and vaginal wall on the infant's head during prolonged labor. The borders are not well-defined and the swelling crosses suture lines since the fluid accumulates outside the periosteum. Cephalohematoma is a subperiosteal hemorrhage caused by the rupture of the emissary or diploic veins of the skull during a prolonged labor and delivery. The margins of the suture lines are clearly demarcated, almost always unilateral, and the swelling never crosses suture lines. It is seen more commonly in vacuum-assisted vaginal deliveries. Estimates of underlying skull fractures range from 5% to 25% (Jensen & Galbraith, 2015).

Forceps marks are identified by their rounded contours and position. The bruised area should be checked for underlying tissue and nerve damage. Scalp lacerations can occur in many ways. A laceration can be caused by the placement of an internal fetal monitoring lead or by the artificial rupture of membranes.

A circular red or ecchymotic area may be caused by the use of a vacuum extractor. Any abraded area may serve as a portal of entry for infection; therefore, a scalp laceration should be carefully and continuously assessed for the presence of infection.

Lacerations can also occur to other body surfaces from scalpel injuries during cesarean birth; an incidence of 1.9% was noted in a series of 896 cesarean section deliveries. Usually the laceration or abscess remains confined to the skin; however, reported complications include osteomyelitis.

Internal fetal monitoring sites are at risk for infection, owing to the introduction of the maternal vaginal flora directly into the subcutaneous tissue of the fetus. Scalp abscesses caused by implantation of a fetal electrode are generally benign, self-limited occurrences. Rare instances of major complications have been reported, however—including significant areas of cellulitis, osteomyelitis, and sepsis (Jensen & Galbraith, 2015).

Subcutaneous fat necrosis is an uncommon subcutaneous tissue disorder that occurs primarily in full-term and postterm infants. It has been associated with birth trauma, shock, asphyxia, hypothermia including therapeutic hypotheria, seizures, and peripheral circulatory collapse. One or several indurated, violet or red plaques or sharply defined subcutaneous nodules on the buttocks, thighs, back, cheek, or arms may appear (Hoath & Narendran, 2015). Hypercalcemia has been associated with subcutaneous fat necrosis so serum calcium levels should be monitored. Most areas of subcutaneous fat necrosis gradually reabsorb over weeks to months if left alone. Residual atrophy or scarring is unusual.

Sclerema neonatorum may have the same cause and adipose tissue abnormality in the subcutaneous tissues as those noted in fat necrosis. However, sclerema more commonly affects the premature or debilitated infant. It is a diffuse hardening of the subcutaneous tissue that results in cold, nonpitting skin. The extremities may be involved at first but generalized involvement occurs within 3 to 4 days. Infants with this disorder are usually critically ill and there is a high mortality rate. If the infant survives, the sclerodermatous changes rarely last beyond 2 weeks. Treatment is based on therapy for the underlying systemic disease, restoration of body temperature, and adequate nutrition. Exchange transfusions and systemic administration of steroids have been used with unconfirmed efficacy (Hoath & Narendran, 2015).

TRANSIENT SKIN LESIONS

Erythema toxicum neonatorum, the most common rash of newborns, usually occurs within 5 days of birth and affects approximately half of term infants, although it is almost never seen in premature infants or those weighing less than 2,500 g. It appears as small, firm, white, or pale yellow pustules with an erythematous margin. Lesions may first appear on the face and spread to the trunk and extremities, but may appear anywhere on the body, except the soles and palms (Howard & Frieden, 2015). Macules, papules, and pustules are seen in varying combinations. A smear and Wright's stain of the pustules reveal numerous infiltrates of eosinophils that are devoid of bacteria. The differential diagnosis includes transient neonatal pustular melanosis, candidiasis, staphylococcal pyoderma, and miliaria. No treatment is necessary.

Neonatal and infantile acne are two distinct conditions distinguished by the time of onset and clinical features. Neonatal acne (neonatal cephalic pustulosis) involves inflammatory, erythematous papules and pustules located primarily on the cheeks, often scattered over the face and extending into the scalp. Usual age of onset is days to weeks. Treatment with low potency topical corticosteroids such as hydrocortisone or imidazole creams such as ketoconazole can result in quicker resolution (Howard & Frieden, 2015). Infantile acne is considered to result in hyperplasia of sebaceous activity. It is found primarily on the face and presents after 1 month of age. Infantile acne can persist for months to years but generally resolves without treatment. Infantile acne may be more persistent and even cause scarring. Some experts suggest that neonatal acne is related to sebum excretion rate while the infantile form is related to high androgen levels but both have genetic influences (Herane & Ando, 2003).

Transient neonatal pustular melanosis is a lesion that is similar to miliaria but is present at birth, usually causing the infant to be unnecessarily isolated. It occurs most commonly on the forehead, behind the ears, and on the palms of the hands and the soles of the feet of term infants. It is most commonly seen in black infants. The differential diagnosis includes *erythema toxicum neonatorum*, staphylococcal impetigo, congenital candidiasis, *miliaria crystallina* or rubra, and acropustulosis of infancy. If the lesions are ruptured, smeared on a slide, and stained, the contents are found to be amorphous debris. The lesion is neither infectious nor contagious. It is self-limiting and requires no treatment.

Sucking blisters that contain sterile, serous fluid may be seen on the thumb, index finger, wrist, or lip. Presumably the result of vigorous sucking in utero, they are seen in approximately 1 in every 250 live births, and resolve without treatment (Howard & Frieden, 2015).

Pigmentary Lesions

Hyperpigmented lesions may be present at birth or during the first weeks of life. Some pigmentary problems are benign, such as mongolian spots, whereas others can be signs of a systemic or genetic disorder. Some of the more common ones are included in this section.

Café au lait spots are irregularly shaped, flat, oval lesions. Their color resembles coffee to which milk has been added. They are present in up to 20% of infants usually over the buttocks. They should be noted on the newborn's initial physical examination; if they are larger than 4 to 6 cm or if more than six are present, a diagnosis of neurofibromatosis should be considered (Hoath & Narendran, 2015). Pigmented lesion lasers can provide a safe and effective therapy for removing café-au-lait spots (Mavropoulos & Cohen, 2013).

Mongolian spots are a collection of melanocytes deep in the dermis. Commonly located over the buttocks and sacrum, they are gray, slate blue, or black in color. They appear in 13% of Caucasian, 65% of Latino, 86% of Asian, and 96% of African American infants (Lucky, 2015).

Hyperpigmentation that presents in a diffuse pattern is unusual in the newborn. When present, congenital Addison's disease,

hepatic or biliary atresia, metabolic disease (Hartnup disease, porphyria), nutritional disorders (pellagra, sprue), hereditary disorders (lentiginosis, melanism), or unknown causes (the bronze discoloration seen in Niemann–Pick disease) may be the cause. Hyperpigmentation of the labial folds with clitoral hypertrophy may result from the transplacental passage of androgens (Dinulos & Darmstadt, 2005).

Neonatal/infantile hypopigmentation results from a diverse group of conditions. It can occur due to any defect in melanocyte development, melanin synthesis and transport, or distribution of melanosomes to keratinocytes. Hypopigmentation can present as a generalized, diffuse, or localized loss of pigment in the neonate which may stem from metabolic (phenylketonuria), endocrine (Addison's disease), genetic (vitiligo, piebaldism, tuberous sclerosis, albinism), traumatic, or postinflammatory causes (Dinulos & Darmstadt, 2005).

Albinism refers to a group of genetic disorders involving abnormal melanin synthesis during embryogenesis (Chan & Tay, 2015). It may occur in any race, with the incidence approximately 1 in 20,000, with a slightly higher rate in African Americans (Sethi, Schwartz, & Janniger, 1996). An autosomal recessive gene usually causes it but rare cases of autosomal dominant inheritance have occurred (Dinulos & Darmstadt, 2005).

Partial albinism (piebaldism) is a localized, autosomal dominant disorder present at birth and easily detected in the dark-skinned infant. Off-white macules are seen on the scalp, widow's peak, and forehead and extend to the base of the nose, trunk, and extremities. A white forelock, a tuft of white hair over the midfrontal scalp, is present in 80% to 90% of patients and is associated with depigmentaion of the underlying scalp (Chan & Tay, 2015). When illuminated with a Wood light, the amelanotic areas of piebaldism exhibit a brilliant whiteness. Differential diagnoses are Waardenburg syndrome, vitiligo, *nevus anemicus*, Addison's disease, and white macules of tuberous sclerosis. Photoprotection of the depigmented areas beginning early in infancy is important to protect from sunburn and to avoid skin cancers later in life.

White leaf macules are the earliest cutaneous manifestations of tuberous sclerosis, an autosomal dominant neurocutaneous syndrome with both cutaneous and neurologic abnormalities (Chan & Tay, 2015). The macules vary in size and shape but most often resemble a mountain ash leaflet. They may be difficult to see in a newborn infant and may be more readily observed by examination with a Wood lamp, which heightens the contrast between the macule and normal skin. Normal infants occasionally have a single lesion but the presence of one or more of these macules in an infant with neurologic problems strongly suggests the diagnosis of tuberous sclerosis. Retinal hamartomas, cardiac rhabdomyomas, and benign renal tumors are some of the other possible findings. A careful family history, detailed physical examination, and multidisciplinary management are indicated in infants with these lesions.

Waardenburg syndrome is a rare autosomal disorder characterized by depigmented patches of skin and hair, congenital nerve deafness, craniofacial anomalies, and heterochromia iris.

Dermatologic Diseases

Diseases of the skin in newborns often present patterns different from the presentation of the same disease in adults. Therefore, a careful physical examination of the skin is necessary for an accurate dermatologic diagnosis to be made. All lesions should be described and their locations and patterns noted.

Lesions can be classified as either primary or secondary. Primary lesions are described as the initial or principal lesions identified when the disease begins. Primary lesions are classified as macule, patch, papule, plaque, nodule, tumor, vesicle, bulla, wheal, pustule, or abscess. Some conditions that present with blister and pustules can be life-threatening (Howard & Frieden, 2015). Secondary lesions are brought about by the modification of a primary lesion resulting in a crust, scale, erosion, ulcer, fissure, lichenification, atrophy, or scar.

Developmental Vascular Abnormalities

The following two major groups of vascular birthmarks are seen:

1. Vascular malformations composed of dysplastic vessels
2. Vascular tumors that demonstrate cellular hyperplasia

Vascular malformations have various subcategories determined by the anomalous vessels involved—including capillary, venous, arteriovenous, or lymphatic. They remain relatively stable in size; any growth is commensurate with growth of the child.

Port-Wine Stain. A port-wine stain is a capillary malformation consisting of dilated and congested capillaries lying directly beneath the epidermis. It appears in approximately 3 out of 1,000 newborns. This birthmark appears pink at birth but gradually darkens to purple. Most commonly found on the face and neck, it is a permanent developmental defect. They are most sharply demarcated and flat in infancy but over time develop a thickened or pebbly surface. Although a port-wine stain is primarily a cosmetic problem, it is occasionally an indicator of a multisystem disorder, such as Sturge–Weber syndrome or Klippel–Trenaunay–Weber syndrome. The presence of seizures, mental retardation, hemiplegia, or intracortical calcification suggests the presence of Sturge–Weber syndrome (Hoath & Narendran, 2015). An ophthalmologic examination is extremely important in these infants. Gradual thickening and nodule formation can occur with port-wine stain and thus support the need for early treatment in infancy and childhood. Although the timing of intervention is somewhat controversial, many dermatologists now advise laser treatment as early as possible in infancy to decrease the stigma associated with this lesion and to prevent skin thickening (Enjolras & Garzon, 2008). Pulsed dye laser is the gold standard for treatment of port-wine stain birthmarks but multiple treatments are required. While laser is effective at fading these lesions, complete resolution is achieved in only 15% to 20% of cases (Hoath & Narendan, 2015; Tremaine et al., 2012).

Pigmented Nevus. Congenital melanocytic nevi are benign nested clumps of melanocytes. In contrast to melanocytes, they tend to lie in groups or nests. Congenital pigmented nevi are different from pigmented nevi that arise later in that they are usually larger and more extensive. As the infant grows, the area becomes thicker and darker (Dinulos & Darmstadt, 2005).

Flat, junctional nevi are seen in about 1% of newborns. They are brown or black and their size varies from one to several centimeters. Conservative management consists of serial observations since there is no evidence that they are a premalignant lesion. Surgical excision may be considered based on location and appearance of the lesion (Hoath & Narendran, 2015).

Large Congenital Melanocytic Nevi. A giant hairy nevus (>20 cm) is characterized by a pigmented and softly infiltrated area. The color varies from pale brown to black. When the nevi are large, they tend to have a dermatomic distribution, and their location and size give them their name (e.g., bathing trunk nevus, vest nevus, shoulder stole nevus; Figure 12.1). On histologic examination of a biopsy specimen, the nevus cells are seen penetrating deeply into the dermis and subcutaneous tissue.

When a giant nevus is situated on the head or neck, it may be associated with mental retardation, epilepsy, or hydrocephalus. *Spina bifida* or meningocele may occur when this nevus is present over the spine (Dinulos & Darmstadt, 2005). Other abnormalities

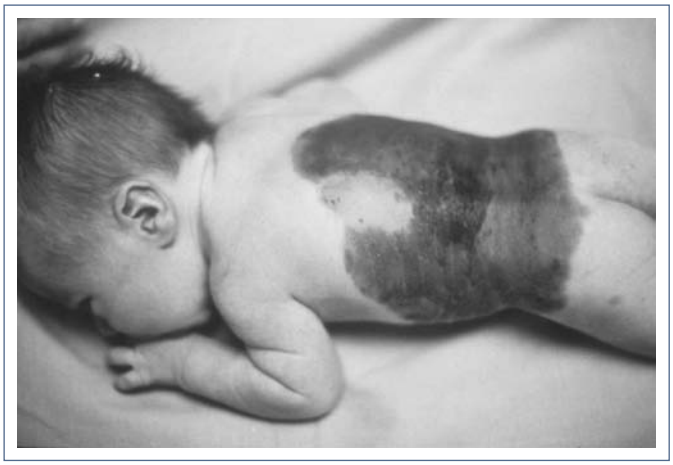


FIGURE 12.1 The giant pigmented hairy nevus of this infant involves the thorax, abdomen, and back and is commonly called a "bathing trunk" nevus. It is raised with fleshy elements and has a somewhat leathery texture.

Source: Reprinted with permission from Clark, D., & Thompson, J. (1986). Dermatology of the newborn, Parts 1 and 2. In *Pathology of the neonate slide series* (Vol. 3, No. 4). Philadelphia, PA: Wyeth-Ayerst Laboratories.

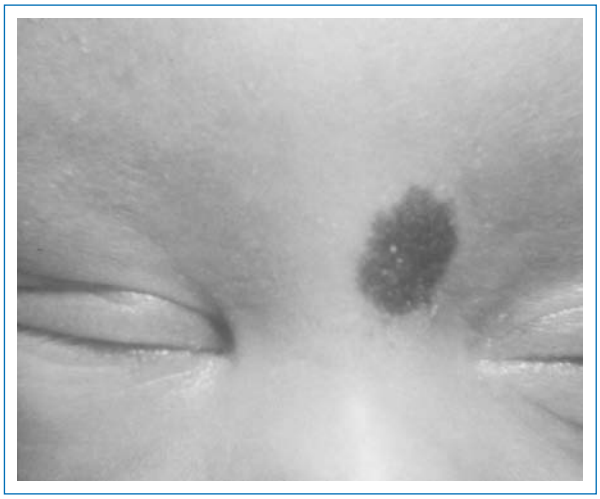


FIGURE 12.2 This photograph shows the early hemangioma in a 28 weeks' gestation premature infant. Approximately 5 weeks after birth the first area of discoloration appeared. The irregular surface with sharp demarcation is typical of strawberry hemangioma, which eventually enlarges to twice the size it appears in this photograph before involution.

Source: Reprinted with permission from Clark, D., & Thompson, J. (1986). Dermatology of the newborn, Parts 1 and 2. In *Pathology of the neonate slide series* (Vol. 3, No. 4). Philadelphia, PA: Wyeth-Ayerst Laboratories.

sometimes associated with a giant pigmented nevus are clubfoot, hypertrophy or hypotrophy of the affected limb, and von Recklinghausen's disease (neurofibromatosis). Besides being a cosmetic problem, the giant nevus is associated with a higher incidence of malignancy. Malignant melanomas develop in as many as 8% of these patients. Management involves surgical excision of the entire lesion to prevent the development of skin cancer in the lesion. Dermabrasion, lasers, and tissue expansion techniques have been used in conjunction with surgery. Plastic surgical reconstruction may be needed if the excision is extensive.

Hemangiomas. Infantile hemangioma (IH) is the most common vascular tumor seen during early infancy. They are characterized by the proliferation of capillary endothelium cells. These cells possess histochemical markers also present in placental vessels (Chen, Eichenfield, & Friedlander, 2013). Hypoxia has been identified as the main factor for vascular proliferation in IH (Laken, 2016). Hemangiomas appear on 1% to 3% of infants at birth and develop on another 10%, usually within the first 3 to 4 weeks of life. Females are 2 to 3 times more likely to be affected than males (Haggstrom & Chamlin, 2014). Besides gender, the other infants at highest risk are non-Hispanic whites, premature infants, and multiple gestation infants. The incidence is 22% in preterm babies who weigh less than 1,000 g and 15% in infants with birth weights of 1,000 to 1,500 g.

Classified by their depth, hemangioma types include superficial, deep, and compound. The treatment for most hemangiomas is "active" nonintervention. Up to 40% will develop complications requiring intervention (Hoath & Narendran, 2015). Congenital hemangiomas that resolve rapidly often leave pronounced atrophic changes in their place.

They most often appear in the skin as a single tumor, but multiple cutaneous lesions also occur, often with involvement of other organ systems.

The natural history of the hemangioma is characterized by its appearance during the first few weeks of life, rapid postnatal growth for 3 to 18 months (proliferative phase), a phase of stabilization for 12 to 18 months, which is followed by very slow but inevitable regression for the next 5 to 8 years (involutive phase; Droitcourt et al., 2018). Infantile hemangiomas completely resolve in more than 80% of children by 4 years of age and continued improvement occurs in the remaining children. The rate of regression does not seem to be related to the sex or age of the infant or to the site, size, or appearance of the hemangioma or the duration of the proliferative phase.

Strawberry or superficial hemangiomas consist of a dilated mass of capillaries in the dermal and subdermal layers that protrude above the skin's surface. They are bright red, soft, compressible tumors that can appear anywhere on the body (Figure 12.2). They generally increase in size for approximately 6 months and then gradually begin to regress or involute spontaneously. Complete involution may take several years to occur. These marks require no treatment but 20% to 40% of patients may have residual skin changes. When these lesions interfere with vital functions such as vision, feeding, and respiration, intervention is required (Enjolras & Garzon, 2008).

Cavernous or deep hemangiomas are more deeply situated in the skin than are superficial strawberry hemangiomas. They are bluish-red, feel spongy when touched, and may not appear until 1 to 3 months after birth. Most hemangiomas are small, harmless birthmarks that involute to leave either normal or slightly blemished skin. However, even a small hemangioma can obstruct the airway or impair vision. A large hemangioma in the liver or an extensive cutaneous hemangioma can divert a considerable volume of blood through its extensive labyrinth of capillaries and produce high-output heart failure. The increased capillary endothelial surface that characterizes a giant hemangioma can also trap platelets and may cause thrombocytopenic coagulopathy as seen in the Kasabach–Merritt syndrome. This syndrome carries significant mortality and requires aggressive treatment such as transcutaneous arterial embolization (Hoath & Narendran, 2015).

A few hemangiomas grow to an alarming size or proliferate simultaneously in several organs and cause life-endangering conditions, such as soft-tissue destruction, deformation or obstruction of vital structures, serious bleeding, ulceration, and sepsis. Large lesions can expand the skin and, even after they regress, result in excess slack skin, pigment changes, and a fibro-fatty residuum.

Visceral hemangiomas may arise in many organs, most commonly in the liver and larynx, with or without cutaneous

involvement; a single lesion or multiple hemangiomas may occur. Having five or more lesions puts the infant at higher risk of a hepatic hemangioma (Laken, 2016). Flow through extensive hemangiomas increases the total blood volume, causes hemodeviation, and disturbs the hemodynamic equilibrium. The hyperdynamic cardiovascular state of the hemangiomas decreases or shunts blood away from other tissues, thus resulting in hypoperfusion of other tissues. This hypoperfusion may cause brain hypoxia, acidosis, and predisposition to seizures, as seen in some cases. Close surveillance of the cardiovascular system is necessary to determine the proper time to begin digitalization.

Large, complex or segmental lesions around the head, neck, lumbosacral, perineal and lower extremities have been associated with congenital anomalies. Large segmental lesions on the face can indicate PHACE syndrome. This neurocutaneous syndrome includes **P**osterior fossa brain formations, **H**emangioma greater than 5 cm, **A**rterial anomalies of head or neck, **C**ardiac abnormalities, and **E**ye abnormalities. Chest wall abnormalities may be present, also (Drolet et al., 2013).

Management. Management of both superficial and deep hemangiomas consists of a detailed history; close scrutiny of the lesion or lesions, including three-dimensional measurements; and evaluation of the growth pattern of the hemangioma. Ulceration, the most common complication that occurs in about 15% to 25% of all infants, can be very painful and result in infection, hemorrhage, scarring, and functional impairment (Hoath & Narendran, 2015). As involution progresses, the color gradually changes from grayish-pink to white or pink and the tension of the lesion decreases. Ulcerated hemangiomas should be treated with topical antibiotics to prevent infection.

While the cutaneous lesions are being monitored, the infant's clinical course and physical development must be closely observed for poor growth, altered cry, stridor, dyspnea, cyanosis, feeding difficulties, or swallowing impairment. **Emergency Alert: If any abnormal sign or symptoms appear—such as tachycardia, heart murmur, hepatomegaly, or bruit that can be *heard* over the liver—the infant should be examined for evidence of heart failure.** Ultrasonography, echocardiography, and computed tomography may be needed.

In general, management consists of planned neglect, which is essential in avoiding disfiguring scars. Complications of therapy may be significant but residual scarring after complete involution is uncommon. Hemangiomas located in exposed areas often cause great parental anxiety, which increases as the hemangioma grows. This anxiety often puts pressure on the physician to do something. However, the hemangioma should be left to regress spontaneously and preconceived notions about birthmarks should be discussed with the family.

In some cases, treatment of hemangiomas may be needed. The following indications for treatment have been proposed: life-threatening or function-threatening hemangiomas, including those that cause impairment of vision, respiratory compromise, or congestive heart failure; hemangiomas occurring in certain anatomical locations such as the nose, lip, glabellar areas, and ear that may cause permanent deformity or scars; large facial hemangiomas, especially those with a large dermal component; and ulcerated hemangiomas (Enjolras & Garzon, 2008).

Alarming hemangiomas is a term used to categorize lesions that impair vital functions or cause life-threatening complications. A vascular mark was present at birth in 68% of these infants. Visceral hemangiomas are associated with cervicocephalic hemangiomas or with small hemangiomas scattered over the body. About a third of these life-threatening hemangiomas respond to treatment with corticosteroids. The mortality rate can be as high as 54% for life-threatening visceral or hepatic hemangiomas and may be up to 30% to 40% with platelet-consumptive coagulopathy, despite the administration of steroids.

High-dose corticosteroid therapy is the primary means of pharmacologically controlling hemangiomas . These agents inhibit the activators of fibrinolysis in vessel walls, decrease plasminogen activator content of endothelium, and increase sensitivity to vasoactive amines, causing constriction of the arterioles. When steroids fail, less conventional modalities, such as embolization, operative excision, pulsed dye laser, interferon-alpha, and sclerotherapy have been used (Smolinski & Yan, 2005).

Vincristine and subcutaneous interferon-alpha-2a (2 MU/m^2 of body surface area) has been used with life-threatening or vision-threatening hemangiomas that failed to respond to corticosteroid therapy. Their mechanisms of action include inhibition of motility and proliferation of endothelial cells and interference with new capillary vessel formation, preventing platelet trapping. These daily injections seemed to reduce the local and systemic complications and appeared to shorten the length of time to involution in some infants. Sustained therapy for 9 to 14 months appeared to be desirable because earlier withdrawal was followed by regrowth of the lesion that was halted and reversed by reintroduction of the drug. Interferon and vincristine have limited use due to their adverse side effects (Chen et al., 2013).

Surgical therapy involving either laser removal or surgical excision is also a treatment option. Excision is usually done once the hemangioma has involuted, so as to remove residual tissue and redundant skin. Early excision is generally not recommended.

Oral propranolol (Inderal) appears to be an effective and safe treatment for infantile hemangioma. It has been shown to decrease the size and reduce the potential for life-long complications.

Emergency Alert: Propranolol had the most significant response when it was started with infants younger than 4 months of age. Potentially harmful effects include hypoglycemia, hyperkalemia, bronchiolitis, bronchospasm, conduction disorders (bradycardia), and hypotension (Droitcourt et al., 2018). The dose should be divided into three daily doses given with a minimum of 6 hours between doses. Giving the dose with, or right after, feeding reduces the risk of hypoglycemia.

The HEMANGIOL study showed that propranolol has a high rate of efficacy with a low rate of serious side effects (Laken, 2016).

Topical management options for infantile hemangiomas includes: Timolol 0.5% gel and corticosteroids. Timolol maleate is a topical beta-blocker that may have a particular role in treatment of superficial lesions. The recommendation is to apply one drop twice a day to affected lesions (Chen et al., 2013).

Blistering Diseases

Epidermolysis Bullosa. Epidermolysis bullosa (EB) is a group of rare, congenital blistering disorders, all of which are inherited. They are considered mechanobullous diseases, meaning that trauma to or friction on the skin induces blister formation. EB is caused by defects in the complex meshwork of proteins in the epidermis, dermis, and dermoepidermal junction that allow the skin to adhere in the presence of frictional stress. The underlying defect appears to be a lack of cellular glue in squamous epithelium, responsible for the maintenance of cellular integrity. Diagnostic studies should include a skin biopsy for light and electron microscopy and immunofluorescence mapping. In all forms of EB, gentle rubbing will result in blister formation, the Nikolsky sign.

EB is classified into three major subtypes by the clinical extent and ultrastructural level of blistering, by inheritance pattern, and

by specific genetic mutations (Hoath & Narendran, 2015; Püttgen & Cohen, 2013). Although some subtypes of EB are severe in the neonatal period and milder later, others can be fatal in the first weeks as a result of severe generalized blistering and complications that arise from this. EB can be nonscarring or scarring. Inheritance may be either autosomal dominant or autosomal recessive.

EB simplex is the mildest form of EB. Most cases are autosomal dominant. The lesions occur at the basal layer of epidermis and do not lead to scarring and hyperkeratosis. Usually present at birth, the vesicles and bullae appear over the joints and the bony protuberances and at sites subjected to repeated trauma.

Junctional EB is a very severe but the least common type of EB with autosomal recessive inheritance. In junctional EB, severe generalized blistering is present at birth, with subsequent extensive denudation. Marked mucosal blistering occurs, and erosions of the larynx, respiratory, gastrointestinal, and urinary tract may also be present. It may be fatal in a few days to a couple of years because of significant loss of electrolytes and protein or sepsis. Histopathologically, a separation occurs between the plasma membrane of the basal cells and the basal lamina at the dermal-epidermal junction (Püttgen & Cohen, 2013). In junctional EB, healing is poor, and scarring is extensive.

Dystrophic or scarring EB results in blistering that occurs below the dermoepidermal junction and has either dominant or recessive inheritance. In the recessive form, blistering, infection, and scar formation can be severe; begins before birth; and can lead to severe deformities and joint contractures. Milia may mark the healed blister sites. Complications include infections and hemolytic, nutritional, orthopedic, gastrointestinal, and psychiatric sequelae. Squamous cell cancer is also associated with this life-limiting type of EB.

The dominant form of dystrophic EB is milder, with less severe blisters or red plaques seen on the distal extremities and bony protuberances (Figure 12.3). Some scar formation occurs and the nails may be mildly dystrophic but deforming scars and contractures occur infrequently. The external skin layer can be easily rubbed off by slight friction or injury. Milia, due to a functional disorder of the sweat glands, are found on the rims of the ears, the dorsa of the hands, and the extensor surfaces of the arms and legs. The oral, anal, and esophageal mucosa are frequently involved but not severely.

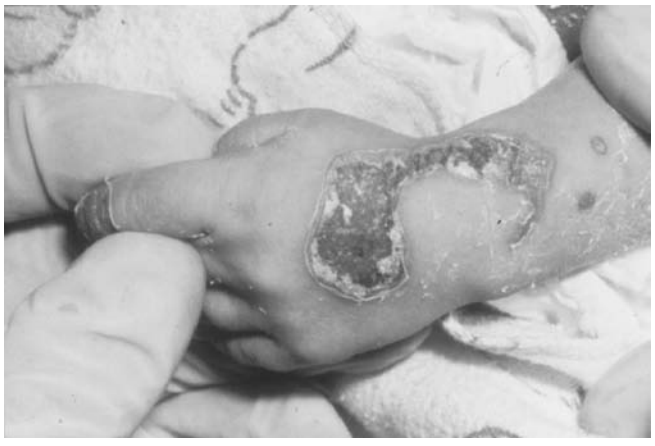


FIGURE 12.3 This photograph of epidermolysis bullosa shows the scaling, broken bullae with underlying erythroderma.

Source: Reprinted with permission from Clark, D., & Thompson, J. (1986). Dermatology of the newborn, Parts 1 and 2. In *Pathology of the neonate slide series* (Vol. 3, No. 4). Philadelphia, PA: Wyeth-Ayerst Laboratories.

Management. EB can be a great challenge in the newborn period, particularly with the more severe forms. Nursing care centers around three main issues: (1) skin breakdown, (2) prevention of secondary infection, and (3) dysphagia. Many of the techniques used to protect the skin of very premature infants are useful with EB patients. Avoiding the use of tape and preventing traumatic injuries is important. Clean, soft dressings may be helpful over bony pressure points. Wound care involves providing a moist healing environment by covering open lesions with a thick coating of petrolatum-based emollients combined with topical antibiotic ointments and covering with nonstick dressings.

Many dermatologists will rotate topical antibiotics every few months to prevent resistance and may use wound cultures to guide selection of agents. Nonstick dressings include petrolatum gauze, Vigilon, Exu-dry, or silicone-based products such as Mepitel (Direct Medical Inc., Houston, TX). After this layer, wrapping with nonadhesive cotton gauze further protects the wound; some practitioners prefer cotton mesh, and others use Coban (3M, Indianapolis, IN), a wrap that adheres to itself without adhesives. When blisters are tense and fluid-filled, they should be "unroofed" to prevent extension. This procedure is done with sharp, clean scissors, leaving the blister roof in place. Dressings are changed daily and removed gently; some prefer to remove dressings during immersion bathing.

From birth to 6 months of age, the environment is easy to control through the use of sheepskin, loose-fitting clothes, and mittens for the infant's hands and feet. Cloth diapers softened with fabric softener are preferred over rougher, disposable diapers. Any person handling the infant should avoid wearing jewelry.

Protection of the infant becomes more difficult once the infant is mobile. The infant should always wear long pants; foam rubber pads sewn into the knees help avoid trauma during crawling. Contractures may form quickly as scarring begins to occur. The pathologic increase in elastic skin fiber adds to this process. Gentle range-of-motion exercises lessen contracture formation.

Dysphagia can occur from facial and pharyngeal scarring, which is secondary to erosions on the buccal mucosa, tongue, palate, esophagus, and pharynx. Feedings should be performed slowly and carefully to avoid aspiration and to maintain adequate nutrition. The metabolic needs of these infants are high because of the continuous skin healing and sloughing of epithelium, which results in large protein, fluid, and electrolyte losses. Additional iron may be required to replace chronic blood loss from the skin (Püttgen & Cohen, 2013). Adding more puncture holes to a nipple may help prevent oral mucosal trauma. If oral ulcerations do occur, several weeks of hyperalimentation and high-dose steroid therapy are instituted. Gavage feedings are discouraged because of the possibility of trauma. It is essential that the family receives genetic counseling regarding the inheritance pattern associated with EB; a negative family history does not exclude its occurrence.

Infections of the Skin

Previously, it was thought that after vaginal birth, the skin colonization with microorganisms reflected the mother's vaginal flora and after cesarean section birth without rupture of the amniotic membranes, the skin was sterile. Recent research using DNA sequencing has begun to reveal that the skin microbiome begins in utero (Gregory, 2011). The skin microbiome of vaginally born infants does appear similar to the mother's vaginal flora but the skin of cesarean section births resembles the mother's and caregiver's skin flora (Dominguez-Bello et al., 2010). It now is known that the skin and its normal flora are natural defense mechanisms against invading pathogens. Maintenance of the skin microbiome is essential to the immunological functioning of the skin (Coughlin,

Frieden, & Eichenfield, 2014). A skin surface pH of between 4.0 and 4.5 facilitates the attachment of the "good" commensal bacteria (Telofski, Morello, Mack Correa, & Stamatas, 2012).

In the newborn, an immature immune system, prematurity, stress, and medical and surgical problems contribute to vulnerability and infection. Additionally, most infants in the NICU require a variety of invasive monitoring and diagnostic procedures that allow for breaks in the normally intact physical barrier of the skin, providing direct access to blood and deep tissues (Dinulos & Pace, 2008). The origin of skin infections and skin manifestations of systemic infection can be bacterial, viral, or fungal.

Bacterial. Bacterial skin infections can vary in initial clinical findings and potential for systemic symptoms and sequelae. The pathogen involved and the route of inoculation are two factors that affect the course of bacterial cutaneous infection (Dinulos & Pace, 2008). Types of bacterial skin infections include bullous and nonbullous impetigo, omphalitis, abscesses, and cellulitis. Severe dermatological findings are also seen when endotoxins are released from bacteria, as in the case of staphylococcal scalded skin syndrome.

Staphylococcus Aureus. Infections resulting from *Staphylococcus aureus* (*S. aureus*) are seen in newborns and can result in bullous, crusted, or pustular types of skin lesions. Nonbullous impetigo is a superficial infection localized to the epidermis and is characterized by erythematous, honey-colored, crusted plaques. Bullous impetigo of the newborn involves blisters that originate in the subcorneal portion of the epidermis and are filled with clear or straw-colored fluid. Bullous impetigo often presents during the first 2 weeks of life. Few or many blisters may be dispersed widely over all areas of the body and may rupture easily, thus leaving denuded areas of skin. Bullous impetigo commonly appears on the diaper area, axilla, and periumbilical skin and is predominantly caused by *S. aureus* (Hoath & Narendran, 2015). If the bacteria are later spread via the bloodstream, the infection may result in osteomyelitis, septic arthritis, or septicemia in neonates (Dinulos & Pace, 2008). Isolation of hospitalized neonates is initiated and intravenous antibiotics are generally recommended in neonates after initial blood, blister fluid, and skin cultures are obtained. Treatment is then tailored to the specific organism when the antibiotic susceptibility profile is known.

Management. Medical and nursing management is focused on treatment of the affected infant and on prevention of the spread of infection to other infants, because this condition is highly contagious. Blood cultures should always be obtained before initiating intravenous antibiotics (Hoath & Narendran, 2015). Systemic antibiotics are administered parenterally initially, due to the release of an epidermolytic toxin by *S. aureus*, in bullous impetigo and may be followed by oral treatment once the infection begins to subside. Antibiotics include oxacillin, nafcillin, or methicillin; vancomycin is used if the culture indicated methicillin-resistant *S. aureus*. Topical antibiotics are not indicated for treatment of bullous impetigo. Additionally, mupirocin intranasally is recommended to prevent recurrent impetigo from nasal colonization. Topical antibiotics can be effectively used for nonbullous impetigo if the lesions are not extensive or involving the mouth area. Fluid and electrolyte monitoring is necessary if the denuded areas cover a large surface or if the infant is of low birth weight (Hoath & Narendran, 2015). Compresses of warm saline can be applied to the affected sites. Isolation of the affected infant is necessary to prevent the spread of the infection throughout the nursery.

Scalded Skin Syndrome. Staphylococcal scalded skin syndrome is a severe endotoxin-mediated disease with superficial, widespread blistering often leading to desquamation (Figure 12.4). The bright erythema of this bullous eruption resembles a scald. The erythema usually begins on the face and spreads downward. Multiple sites are cultured when this disease is suspected, including any bullous lesions, blood, cerebrospinal fluid, nasopharynx, urine, conjunctival sac, and umbilicus in an effort to recover an organism. Staph scalded skin syndrome is rarely seen at birth with most cases appearing between 3 and 7 days of life (Hoath & Narendran, 2015).

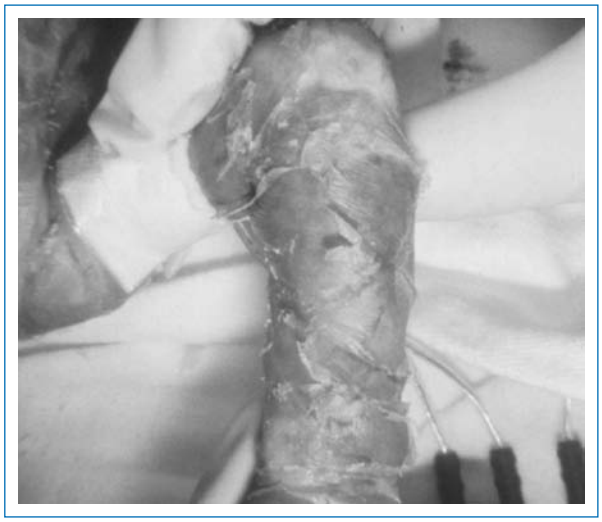


FIGURE 12.4 The peeling, scaling skin of this premature infant had an acute onset at approximately 2 weeks of age. This is the scalded skin syndrome that results from *Staphylococcus aureus*.

Source: Reprinted with permission from Clark, D., & Thompson, J. (1986). Dermatology of the newborn, Parts 1 and 2. In *Pathology of the neonate slide series* (Vol. 3, No. 4). Philadelphia, PA: Wyeth-Ayerst Laboratories.

Skin will appear bright red, like a burn, followed by the development of large, loose blisters that quickly progress to sheets of skin being shed. During the course of this disease, the entire epidermis may be shed. Emollients, together with semi-occlusive dressings, provide gentle lubrication and pain relief.

Management. Medical and nursing management also involves administration of the appropriate systemic antibiotic regimen and supportive measures in terms of fluid and electrolytic replacement, prevention of secondary infection through the damaged epidermis, and pain management. Applying local antibiotic solutions or ointments is not recommended; cleansing open skin areas with gentle irrigation using half normal saline followed by the application of a nonadherent dressing that promotes healing and prevents secondary infection is better (King, Stellar, Blevins, & Shah, 2014). The infant may be more comfortable in an incubator rather than in a radiant warmer because the incubator is a convective heat source that does not have a direct cutaneous effect, whereas the radiant heat source heats directly through the skin. In addition, the radiant heat source may further increase the degree of insensible water loss through the damaged epidermis. Usually, a flaking process is observed on the skin during the healing process. Emollients may be helpful in treating dry skin at this point.

Listeria Monocytogenes. Another bacterial skin disease is listeriosis, caused by *Listeria monocytogenes*. This organism, which can cause severe systemic disease, can also result in a disseminated miliary granulomatosis in neonates (Hoath & Narendran, 2015). In some cases, miliary abscesses can occur, and occasionally, more generalized erythema or petechiae may be present. Systemic listeriosis is a severe infection that causes blood hemolysis and a high mortality rate. Prompt recognition and treatment with intravenous penicillin or ampicillin are indicated for the best prognosis. No direct skin therapy has been described as being necessary in this disease.

Syphilis. Congenital syphilis is another bacterial infection that has skin manifestations. Sixty percent of infants born with congenital syphilis are asymptomatic at birth (Püttgen & Cohen, 2013). If the infant with congenital syphilis is not treated after birth, a maculopapular or bullous skin eruption develops between 2 and 6 weeks of age. Sometimes, the bullous lesions may be observed at birth on the palms or the soles, signifying the presence of more severe disease (Hoath & Narendran, 2015). Fluid contained in the blisters contains spirochetes.

The lesions most commonly seen in congenital syphilis are copper-colored and maculopapular and are located on the soles and palms. In addition, open lesions may be present around the mouth, anus, or genitals, and a highly contagious nasal discharge is occasionally seen. If the syphilis remains untreated, the lesions regress in 1 to 3 months, leaving areas on the skin with either hyperpigmentation or hypopigmentation.

Management. Medical and nursing management for the infant with congenital syphilis involves prompt, consistent administration of penicillin. Titers are obtained over the next year at 3-month intervals, and a negative serologic finding is expected at 1 year. Care of the skin lesions is primarily directed toward preventing the spread of infection during the active phase of the illness, especially when bullous lesions or open areas are apparent. No direct topical therapies have been advocated in the literature.

Viral. Viral infections can display a broad range of cutaneous manifestations in the neonate and can occur in utero, perinatally, or postnatally. Congenital infections are known by the acronym TORCH, which stands for: Toxoplasmosis, Other (syphilis, varicella), Rubella, Cytomegalovirus, Herpes Simplex (Örge & Grigorian, 2015). Skin manifestations can be a direct result of skin infection or be a consequence of viral infection in other tissues. Viral infections that result in cutaneous manifestations include herpes simplex virus, cytomegalovirus (CMV), rubella, varicella, enterovirus, parvovirus, and human immunodeficiency virus. Some of these have very specific cutaneous presentations (such as the classic "blueberry muffin" appearance of infants infected with rubella and cytomegalic virus), vesicles (as with herpes simplex), or nonspecific lesions. Toxoplasmosis, which has cutaneous manifestations and is caused by a parasite, is also discussed in this section.

Herpes Simplex. Herpes simplex virus (HSV) types 1 and 2 are serious pathogens in newborns. Intrauterine herpes infection typically presents with vesicles at birth or within the first 24 hours of life. The majority of newborns acquire infections from infectious vaginal secretions at the time of delivery. The 1- to 3-mm vesicles that occur on the skin with this disease usually develop at 6 to 13 days of life. They can vary; a few faint scars may be present, or actual vesicle formations may be present with either one large swelling or discrete groups of vesicles. Frequently, an inconspicuous cutaneous lesion is a sign of systemic infection (Hoath & Narendran, 2015). Vesicles may recede and then recur over months.

Herpes simplex virus, types 1 and 2, is one of the most serious viral infections to affect the newborn and can appear as disseminated infection, central nervous system infection, and infection localized to the skin, eyes, or mouth. Disseminated infection is the most devastating presentation, with a mortality rate of up to 75% without antiviral therapy, and about 50% if antiviral therapy is used (Friedlander & Bradley, 2008). Vesicle formations may present with either one large swelling or smaller groups of vesicles that crust over rapidly and then recede. Absence of vesicles does not rule out the disease. Management consists of early recognition and treatment with antiviral agents, such as acyclovir, along with isolation from other infants. If encephalitis develops, the prognosis is extremely poor with either a high risk of death or severe mental retardation.

Management. Medical and nursing management is centered primarily on early recognition and treatment with the antiviral medication acyclovir. A definitive diagnosis is made by scraping the base of a fresh vesicle and staining with Giemsa or Wright stain, direct fluorescent antibody staining, or enzyme immunoassay detection of HSV antigens (Püttgen & Cohen, 2013).

The prognosis of systemic herpes simplex is extremely poor if encephalitis develops, with a high risk of either death or severe mental retardation. An important consideration in the care of infants with known or suspected herpes simplex infection is isolation from other patients to prevent transmission.

Varicella. Another viral infection with manifestation in the skin is varicella. Varicella infection is rare, but when it occurs in the first 10 days of life, it is generally thought to have been acquired in the last 3 weeks of pregnancy. The vesicular eruptions are the same as those in chickenpox acquired at any age. A mortality rate of 20% is associated with varicella infection in newborns and this infection poses a significant risk for immunocompromised infants in premature and intensive care nurseries. No systemic medication or topical treatment is required for these lesions. Occasionally, scarring can occur. Strict isolation is absolutely necessary to protect other infants from exposure because this virus is airborne.

Toxoplasmosis. Toxoplasmosis, which is caused by an intracellular parasite (*Toxoplasma gondii*), can be transmitted transplacentally and can result in systemic infection. Some infants may have a generalized maculopapular rash as well as hepatosplenomegaly, jaundice, fever, and anemia. The rash may progress to desquamation and hypopigmentation in very severe cases. Direct topical therapy is not reported to be necessary or efficacious; systemic therapy may be considered.

Cytomegalovirus and Rubella. Both CMV and rubella have symptoms manifested in the skin. Petechial lesions can occur with both infections. These are the result of thrombocytopenia and dermal erythropoiesis and usually disappear in 2 to 6 weeks. In severe rubella infection, and very rarely in CMV, bluish-red papules that are 2 to 8 mm in diameter can occur on the head, trunk, and extremities (Figure 12.5), resulting in the description "blueberry muffin" syndrome. Ocular involvement in congenital rubella is common. The characteristic "salt and pepper" retinopathy is the most common finding, but cataract is responsible for the greatest

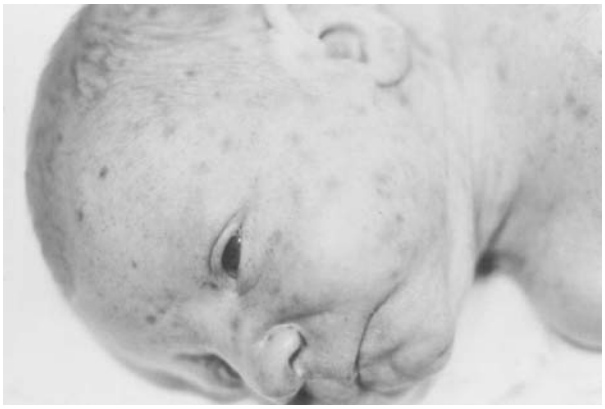


FIGURE 12.5 This is an example of the "blueberry muffin" syndrome, seen in an infant with congenital cytomegalovirus infection. The infant has multiple petechiae and purpura from thrombocytopenia in this systemic infection.

Source: Reprinted with permission from Clark, D., & Thompson, J. (1986). Dermatology of the newborn, Parts 1 and 2. In *Pathology of the neonate slide series* (Vol. 3, No. 4). Philadelphia, PA: Wyeth-Ayerst Laboratories.

vision loss (Örge & Grigorian, 2015). Neither of these lesions requires topical therapy.

Fungal. *Candida albicans* infection is the primary fungal infection with cutaneous manifestations, although other species—such as *Candida parapsilosis*, *Candida tropicalis*, *Candida lusitaniae*, *Candida glabrata*, and Malassezia furfur—can also potentially colonize the skin of term and preterm newborns, particularly those who are hospitalized in an intensive care nursery. On routine screening, roughly one third of healthcare workers in the NICU test positive for *candida* (Hoath & Narendran, 2015). Clinical symptoms of this type of infection can range from diaper dermatitis to other mucous membranes or localized skin eruptions to systemic candidiasis, resulting in significant morbidity and mortality. *Candida* is not normally found on the skin of the newborn. The primary reservoir for this organism is the gastrointestinal and female genital tracts, so the skin can be colonized at birth during passage through the birth canal. The incidence of *Candida* colonization is also increased with the frequent use of broad-spectrum antibiotics that alter normal skin flora in infants after delivery. Nursing assessment of the low-birth-weight infant should include the observation of a monilial diaper rash or a diffuse burn-like dermatitis affecting large areas of the lower back, buttocks, chest, and abdomen (Baley & Silverman, 1988). *Candida* dermatitis is recognized as an early presentation of invasive fungal disease in the extremely-low-birth-weight infant (Benjamin et al., 2010).

Premature neonates with systemic candidiasis may demonstrate cutaneous involvement. This cutaneous pattern may be a diffuse, burn-like dermatitis that affects large areas on the lower back, buttocks, chest, and abdomen. Lesions typically appear in skin creases also (Püttgen & Cohen, 2013). In a few infants, the axilla and groin are affected. Scaling follows the erythematous macular patches and in severe cases desquamation develops in a manner similar to that seen in staphylococcal scalded skin syndrome. These infants do not always have the satellite papules and pustules normally seen with *Candida* diaper dermatitis. The onset of the generalized rash often occurs within the first 3 days to 4 weeks of life but can appear later. Skin biopsies performed on patients with this condition revealed fungal invasion that extended beyond the epidermis into the dermis. Associated factors included maternal colonization with vaginal birth, steroid administration, hyperglycemia, and skin trauma from adhesive removal. Infants who weigh less than 1,500 g are especially at risk for systemic infection. In addition to birth weight less than 1,500 g, risk factors for disseminated candidiasis include respiratory therapy, central line placement, antibiotic use, and parenteral nutrition (Hoath & Narendran, 2015).

Another important cause of necrotic and purpuric lesions in neonates with ecchymoses and crust-like plaques is cutaneous infection with mold species, such as *Aspergillus*, *Fusarium*, *Rhizopus*, and *Mucor* (Hook & Eichenfield, 2011). Biopsy is often part of the evaluation, particularly if surface cultures are not conclusive; cutaneous debridement, along with systemic antifungal agents, may improve outcomes for these rare cases.

Management. Medical and nursing management of infants with systemic or local *Candida* infection involves therapy with systemic antifungal medications and antifungal ointments and creams. Cutaneous *Candida* in the extremely premature infant less than a week of age requires aggressive monitoring for systemic infection and may warrant parenteral antifungal agents to prevent dissemination of the fungal infection. Yeast is sometimes difficult to culture; techniques include obtaining urine to look for hyphae or budding yeast, blood cultures, and skin scrapings prepared with potassium hydroxide (KOH) obtained from the margins of the affected areas since this is the area of active growth, and examined for pseudohyphae (Cunningham & Wagner, 2008). Nursing observation in low birthweight infants for evidence of the diffuse, burn-like dermatitis or a spreading monilial diaper rash is essential and may expedite the initiation of parenteral antifungal therapy for systemic candidiasis. Most candidiasis species found in the NICU are sensitive to fluconazole and amphotericin (Lin et al., 2013).

Treatment for *Candida* diaper dermatitis consists of keeping the area clean and dry and applying an antifungal ointment or cream several times a day. Thrush, an oral fungal infection, appears as patches of white material scattered over the tongue that cannot be scraped off. It is treated with an oral form of nystatin.

Scaling Disorders

A scaly appearance in the skin of a newborn can have a range of causes, from relatively benign to long term and potentially life-threatening. In this section, scaly skin due to postmaturity, essential fatty acid deficiency, congenital ichthyosis, and eczema is discussed and areas of nursing management determined.

Postmaturity. Many term infants born between 40 and 42 weeks' gestation experience a period of shedding or desquamation considered to be a normal physiological process. Postmature infants born after 42 weeks' gestation may also have this appearance but other characteristics are different. The postmature infant may have a lean appearance, with little subcutaneous fat; the weight is low in relationship to length. The skin resembles parchment paper and may literally peel off in sheets, peaking near the eighth day of life (Hoath & Narendran, 2015). Fingernails may be stained with meconium and may be long. Long hair may also be present.

Skin care is not the major problem, nor is it the focus of medical or nursing management. Eventually, the skin underneath the peeling layers predominates; even during the period of desquamation, the skin functions well as a barrier because these infants have all the layers of *stratum corneum* of a term infant or adult. Aside from bathing with a mild baby wash initially, moisturizing with a petrolatum-based ointment may be appropriate. More careful attention is paid to the more compelling problems associated with postmaturity, such as hypoglycemia and meconium aspiration.

Essential Fatty Acid Deficiency. In newborns unable to receive an adequate diet because of other illnesses or surgical conditions, scaly dry skin may signify the development of essential fatty acid deficiency syndrome. Infants may be more prone to the development of this syndrome, especially if they are premature or postmature because of the decreased fat stores available. It may also occur in infants with severe fat malabsorption, such as those with cystic fibrosis.

The skin appearance in essential fatty acid deficiency includes a superficial scaling and, in some cases, desquamation. Later presentation may involve oozing and irritation in the neck, groin, or perianal region.

This syndrome is sometimes confused with other conditions that cause scaling or other skin disruptions, including ichthyosis, acrodermatitis enteropathica, and candidal infection. Laboratory findings that confirm this diagnosis are decreased serum essential fatty acid levels, possibly in conjunction with thrombocytopenia and impaired platelet aggregation, because essential fatty acids are necessary to ensure platelet function.

Management. Medical and nursing management consists of replacement of essential fatty acids through the administration of intravenous lipid solutions or diet. Human breast milk and most infant formulas contain more than adequate amounts of essential fatty acids. However, if the gastrointestinal system is not

functioning well in the digestion and absorption of nutrients, intravenous therapy is required.

Once skin symptoms are present, administration of intravenous lipid solution can reverse the process in 1 to 2 weeks. Dietary replacement takes longer and is effective only in the presence of healthy gastrointestinal function.

Prevention of essential fatty acid deficiency is possible and should be the goal. The development of essential fatty acid deficiency can be prevented by the early administration of intravenous lipid solutions in the first weeks of life in a dose as low as 0.5 g/kg/day.

Ichthyosis. The most serious cause of dry, scaly skin in the newborn is ichthyosis dermatosis, a genetically inherited disorder of cornification (Ivich, 2015). Four major types of ichthyosis exist: (1) X-linked ichthyosis; (2) lamellar ichthyosis; (3) bullous congenital ichthyosiform erythroderma, which is present at birth; and (4) *ichthyosis vulgaris*, which usually appears after the third month of life. Terms commonly used to describe infants with ichthyosis may include harlequin fetus and collodion baby, but these terms do not define which form of ichthyosis is present.

In the X-linked type of ichthyosis, males are primarily affected. Some female heterozygotes may exhibit mild scaling of the arms and lower extremities. Affected male newborns have large yellow or brown plaques that cover the whole body, except the palms, soles, and midface, and over joints. At birth, some affected males may appear scaly, whereas others are often called collodion babies.

Lamellar ichthyosis, formerly called nonbullous congenital ichthyosiform erythroderma, is an autosomal recessive disorder. Initially, affected newborns may have a bright red appearance that rapidly progresses to desquamation; rarely is a collodion-baby appearance present at birth. Later, scales develop that are yellow to brown and that may eventually become thick, horny plates. Although the prognosis is usually good, infants who are severely affected with the most severe form—harlequin ichthyosis—may die of sepsis or require extensive plastic surgery (Figure 12.6). Among them, difficulties faced are eye disease, heat intolerance, finger contractures, chronic skin infections, and hearing problems (Ivich, 2015).

In bullous congenital ichthyosiform erythroderma, autosomal dominance is the mode of heredity; thus, several family members may be affected. Large bullae are initially seen, as are erythema and dry scaly skin; the blistering that recurs throughout childhood differentiates this form from the lamellar type. Extensive denuded areas of the skin can present a problem in the newborn as the blisters burst and secondary life-threatening infections with *Streptococcus* or *Staphylococcus* can occur.

FIGURE 12.6 This harlequin infant is an example of the most severely affected ichthyotic infant. The skin is hard and thick, with deep crevices. The lack of elasticity of the skin results in fleshy deformities of joints and limbs.

Source: Reprinted with permission from Clark, D., & Thompson, J. (1986). Dermatology of the newborn, Parts 1 and 2. In *Pathology of the neonate slide series* (Vol. 3, No. 4). Philadelphia, PA: Wyeth-Ayerst Laboratories.

Management. Medical and nursing management of X-linked and lamellar forms of ichthyosis involves the continual use of topical emollient, prescription bathing techniques, and the prevention of infection. **Quality and Safety: Emollients increase hydration and help restore barrier function; keratolytics, used after the newborn period, assist in scale shedding.** Bathing is performed with water-dispersible bath oil, and soaps that are excessively drying or irritating should be avoided. Collodion babies should be placed in a high-humidity incubator to increase hydration. Emollients that preserve moisturization such as Aquaphor ointment (Beiersdorf, Inc., Wilton, CT) should be applied several times daily.

Infants with severe skin involvement from ichthyosis may require protective isolation if they receive care in an intensive care nursery because of the higher risk of contact with nosocomial infections. Incubators provide a barrier to infection. Use of sterile linen and sterile gloves and other measures are needed if larger areas of denuded skin are present. Nutrition management is important due to the infant's high metabolic demands from inflammation, evaporative calorie losses, and cutaneous hyperplasia.

Multidisciplinary involvement of genetics, ophthalmology, dermatology, and physical therapy is essential to care. Comfort is another key nursing concern in the care of the infant who is significantly affected with ichthyosis. Fussy, irritable agitation may be seen and is related to pruritus or inflammation. Some form of analgesia may help, although the topical therapies prescribed have the most direct effect. Some authors describe the use of diphenhydramine (Benadryl, Pfizer, Morris Plains, NJ) if severe pruritus exists but this would be hard to determine in a neonate who lacks verbal or fine motor skills to communicate this symptom. A trial of this medication with careful observation might be helpful in the case of a frantic or irritable infant when other measures (e.g., topical treatment, pacifiers, feeding) are unsuccessful.

Working with the parents of an infant with ichthyosis has many facets. The appearance of the infant, especially if he or she is severely affected, could be shocking and traumatic to the parents and could require careful interventions. As with parents of infants with other congenital abnormalities, a period of shock, denial, and grief occurs over the loss of a perfect baby. In addition, the genetic nature of this disorder and the implications for future children must be comprehended. Parents of these infants need genetic counseling, support, and education as they come to terms with this disease.

Eczema. Atopic eczema (AE) or atopic dermatitis (AD) is a skin disorder that causes several degrees of skin irritation and has multiple causes but is rarely seen in the newborn period. It is more commonly seen within 3 months of age and involves an eruption that proceeds to the development of microvesicles and oozing, which later turns into scaling of the epidermis (Blume-Peytavi & Wahn, 2011). The scaling is due to an attempt of the skin layer to regenerate rapidly. Lichenification, or thickening of the skin, which occurs in adult skin with eczema, is not seen in infants.

Epidermal barrier dysfunction has been shown to be a contributing factor in AE. Studies have shown that maternal AE (and to a lesser extent paternal and sibling history) was a risk factor for the development of AE in infants (Deckers et al., 2012). Prevalence of food allergy has been reported to be between 20% and 80% in infants who develop AE (Newland, Warren, & Gold, 2013).

Primary irritants—such as saliva, feces, and some soaps or skin preparations—rather than allergies are the usual causes of irritant

contact dermatitis in infants (de Waard-van der Spek et al., 2013). However, it is important to have a good history of all products that have been applied to the skin to determine the cause.

Management. Improving skin barrier function early in life through the daily application of topical emollients may reduce sensitization and prevent the development of AE along with food allergies and asthma (Simpson, Berry, Brown, & Hanifin, 2010). Medical and nursing treatment of eczema also includes prevention by avoiding the primary irritant source, if it has been identified, or protection, as in the use of zinc oxide paste to the perianal area to prevent contact with feces. Short-term therapy with topical steroids may be used for more generalized eruptions.

Bathing should be carried out in lukewarm water with a synthetic surfactant-based cleanser with a pH of 5.5 to 6.0; use of irritating or drying soaps should be avoided (Telofski et al., 2012). The effectiveness of any emollient increases if it is applied directly after bathing to seal in the humidity (Fernandes, Machado, & Oliveira, 2011). If large areas of skin are involved, thermoregulation may be a concern, especially in dry climates. Humidification may be desirable in some climates, especially during the summer months. Air conditioning may also be necessary during the summer months. Discomfort is a significant concern because infants with eczema may experience considerable pruritus. Topical therapy is generally the first consideration, followed by the judicious use of diphenhydramine in severe cases.

SKIN CARE PRACTICES

The most basic aspects of skin care for newborns include bathing; moisturizing with emollients; skin preparation with disinfectant solutions; and use of medical adhesives for life-support devices, monitoring of vital signs, and oxygenation, if the newborns are hospitalized. During all these practices, the skin of the newborn has the potential for trauma or alterations in normal barrier function and pH. The literature is reviewed to determine what is currently known about these and other common nursing practices and the impact on the skin of newborns.

Bathing

First Bath

The purpose of bathing newborns includes providing overall hygiene, aesthetics, and protection of healthcare workers by removing blood and body fluids. However, bathing is not an innocuous procedure, and during the immediate postbirth period it can result in hypothermia, increased oxygen consumption, and respiratory distress. There is ongoing debate about when the first bath should be given and even whether to bathe the newborn at all (Colwell, 2015). The Neonatal Skin Care Evidence-Based Clinical Practice Guideline, developed by the AWHONN, recommends giving the first bath when thermal and cardiorespiratory stability has been achieved, between 6 and 24 hours of age (AWHONN, 2018). The WHO recommends delaying the bath for 24 hours, or, if this is not possible due to cultural reasons, waiting at least 6 hours in an effort to prevent hypothermia, especially in developing countries (WHO, 2015). However, infants born to a mother who is HIV positive should be bathed as soon as possible after delivery once their temperatures have stabilized (Kilpatrick, Papile, & Macones, 2017).

Techniques for giving the first bath include sponge bathing with a small tub such as those provided in the hospital, or an immersion bath in a larger tub. Immersion bathing places the infant's entire body, except the head and neck, into warm water (37.8°C–38.8°C), deep enough to cover the shoulders. Studies involving over 1,000 newborns report that tub or immersion bathing, compared to sponge bathing, maintains temperature better, causes less crying and distress for the infant, and does not result in increased infection, even with the umbilical cord in place (G. C. Anderson, Lane & Chang, 1995; Bryanton, Walsh, Barrett, & Gaudet, 2004; Cole, Brissette, & Lunardi, 1999; Hennigsson, Nystrom, & Tunnel, 1981). In a study of 100 late preterm infants (35–36 6/7 weeks' gestation) randomized to immersion tub bathing or sponge bathing after 24 hours of life, infants had overall higher temperatures and less variability in body temperature when immersion bathed (Loring et al., 2012).

Using a swaddle cloth during bathing adds additional comfort for the newborn. A randomized controlled study of providing this support for full-term newborns during their first bath found swaddled bathing was more effective in maintaining temperature, as well as other physiological parameters such as heart rate and oxygen saturation (Çaka & Gözen, 2017). There has also been the benefit of reducing parental stress during swaddle bathing (Fern, Graves, & L'Huillier, 2002).

The Neonatal Skin Care Guideline recommends using warm tap water with or without a mild cleansing bar or liquid cleanser that has a neutral or slightly acidic pH to assist in the removal of blood and meconium, as water alone may not easily remove some lipid-soluble substances such as meconium. For premature infants less than 32 weeks, warm water only during the first week of life is the recommendation (AWHONN, 2018),

Leaving residual *vernix caseosa* on the skin is important, as vernix facilitates skin adaptation including skin hydration and the formation of the acid mantle of the skin surface (Visscher et al., 2005). WHO guidelines for newborn care recommend leaving vernix intact for at least 6 hours (Visscher & Narendran, 2014; WHO, 2015).

Routine Bathing in NICU Patients

A number of issues surround determining the optimal frequency of bathing and best techniques for administering the bath for hospitalized neonates. The NICU population can range from full-term infants with illness, infection, or the need for surgical interventions to extremely low birth weight premature infants.

Knowledge about the impact of bathing on neonatal skin barrier function as measured by parameters such as skin surface pH, transepidermal water loss (TEWL), and hydration of the *stratum corneum* (SCH) is important to inform practice. Bathing has the potential to alter the development of the acid mantle of the skin. On the first day of life, the skin surface pH is greater than 6.0, falling to less than 5.0 during the first weeks of life (Behrendt & Green, 1971; Hoeger & Enzmann, 2002; Yosipovitch et al., 2000). Premature infants' skin develops an acidic surface, reaching a pH of 5.5 at the end of the first week, and 5.0 by the end of the first month (C. Fox et al., 1998). Once the acid mantle of the skin surface is established, bathing can transiently alter the skin pH, even with water alone, in older infants (Gfatter, Hackl, & Braun, 1997). Bathing two to three times per week with cleansing products compared to water alone has been shown to have little or no difference on skin pH, TEWL, and SCH in the neonatal period in full-term healthy infants (Dizon, Galzote, Estanislao, Matthew, & Sarkar, 2010; Garcia Bartels et al., 2010; Lavender et al., 2012). Similar studies involving measuring skin parameters have not been performed in hospitalized neonates or in premature infants.

Sponge and tub bathing in premature infants can negatively impact physiological parameters such as heart rate, oxygenation, and behavioral cues indicating distress with bathing (Liaw, Yang, Yuh, & Yin, 2006; Peters, 1998). Because of the concern about the stress on premature infants during bathing, researchers evaluated the impact of bathing with a mild cleanser every 2 versus

4 days on normal skin colonization and on pathogenic bacteria (Quinn, Newton, & Piecuch, 2005). Although an initial decrease in bacterial skin colonization was noted, bacterial colonization was restored at 48 hours and remained stable between 48 and 96 hours after bathing. Another study reported a transient decrease in skin colonization in premature infants of 28 to 35 weeks' gestation with coagulase-negative staphylococcus at 30 minutes following the bath, regardless if the bath was given with water alone or water and liquid soap (da Cunha & Procianoy, 2005). It does not appear that decreased bathing frequency from every 2 days to 4 days in premature infants leads to an increase in skin colonization, and the use of bathing products or water also does not increase skin colonization with coagulase negative staphylococcus. Therefore, less frequent bathing will subject premature infants to less physiological and behavioral stress. Swaddling the premature infant during routine bathing was shown to reduce temperature loss and crying (Edraki, Paran, Montaseri, Razavi Nejad, & Montaseri, 2014), and hand containment and postural support reduce stress as well (Liaw, Yang, Chou, Yang, & Chao, 2010).

Emollients

The skin surface of term newborns is drier than that of adults but becomes gradually better hydrated as the eccrine sweat glands mature during the first year of life. Maintaining the hydration of the *stratum corneum* is necessary for an intact skin surface and normal barrier function. Skin that is dry, scaly, or cracking is not only uncomfortable but also can be a portal of entry for microorganisms.

Treatment for dry skin includes moisturizers or emollients. Emollients are classified as oil-in-water (ointments) or water-in-oil emulsions (creams, lotions). Ointments do not require a preservative whereas creams and lotions do require preservatives due to the higher water content (Hoath & Narendran, 2000).

Several studies have evaluated emollient use in premature infants. Premature infants of 29 to 36 weeks' gestation were treated with a cream moisturizer twice daily and had less visible dermatitis but no change in skin barrier function (Lane & Drost, 1993). A randomized controlled trial of younger gestation premature infants receiving twice daily applications of a petrolatum ointment versus routine skin care reported improvements in skin barrier function, measured as a lower TEWL and less visible dermatitis. No increases in skin temperature or redness were seen if the infants were receiving phototherapy or cared for under radiant warmers and no increase in bacterial or fungal cultures was reported. In addition, although there were not enough subjects to verify this outcome, the treated infants had fewer positive blood or cerebrospinal fluid cultures (Nopper et al., 1996).

A large randomized controlled trial of 1,191 extremely low birth weight infants (510–1,000 g) was undertaken to determine if the twice daily prophylactic application of petrolatum-based ointment would reduce the combined outcomes of mortality and sepsis (Edwards, Conner, & Soll, 2004). No effect was seen in these combined outcomes, although skin integrity appeared improved in the treated infants. It is important to note that in infants less than 750 g, the incidence of bloodstream infections with coagulase-negative staphylococcus was increased in the group with prophylactic use of the emollient, although the mechanism and relationship to twice daily emollient use are not clearly understood. The control infants in this study also received emollients on an "as needed" basis for skin dryness.

A Cochrane review evaluated RCTs of emollient use in the NICU and concluded that the prophylactic application of topical ointment increases the risk of coagulase-negative staphylococcus infection as well as other nosocomial infections. The routine use of emollients in preterm infants is not recommended (Conner, Soll, & Edwards, 2004).

The benefits of emollient use in premature infants must be carefully weighed against the risk of infection. In general, emollients can be safely used in this population to treat skin with excessive drying, skin cracking, and fissures. They may also be beneficial in reducing TEWL and evaporative heat loss, although methods such as using a high-humidity environment are also available for this purpose. Small tubes or jars for single patient use are recommended to prevent contamination with microorganisms.

There is little consensus to date about the routine use of emollients for full-term newborns (Irvin & Miller, 2015). One study reports improved skin parameters in healthy full-term infants when the skin care regime included a "baby cream" emollient after bathing and did not adversely affect bacterial skin colonization (Garcia Bartels et al., 2010). However, promising studies report a decreased risk of developing atopic dermatitis in infants with a strong family history of this disorder with daily use of emollients in infancy, so the routine use of emollients may be indicated in this population (Horimukai et al., 2014; Simpson et al., 2014).

Skin Disinfectants

Use of skin disinfectants prior to invasive procedures such as inserting intravenous lines, venipuncture, arterial puncture, umbilical catheter placement, and chest tube placement is common practice in neonatal nurseries. Concerns with disinfection practices include the effects of absorption of disinfectants and skin injury resulting from topical skin preparation with these agents, which must be weighed against their effectiveness in preventing infection.

Disinfectants that are used in newborns include 70% isopropyl alcohol (IA), 10% povidone-iodine (PI), and chlorhexidine gluconate (CHG), in varying concentrations as both an aqueous solution and one combined with 70% isopropyl alcohol (CHG/IA). It is widely accepted that CHG-containing formulations are the most effective for skin disinfection in children and adults for central venous catheter insertion and dressing changes and their use is recommended as best practice in several guidelines (Chaiyakunapruk, Veenstra, Lipsky, & Saint, 2002; Loveday et al., 2014; Marschall et al., 2014). However, there are no studies in neonates that have confirmed the superior efficacy of CHG preparations over other disinfectants, such as PI, in the prevention of bloodstream infection (Ponnusamy, Venkatesh, & Clark, 2014; Sathiyamurthy, Banerjee, & Godambe, 2016). Therefore, the Centers for Disease Control and Prevention (CDC) guidelines have maintained that there is insufficient evidence to make a recommendation about the safety or efficacy of CHG products in infants younger than 2 months of age (O'Grady et al., 2011).

Use of 0.5% CHG in isopropyl alcohol reduces peripheral IV catheter colonization in premature and term newborns compared with use of povidone-iodine (Garland et al., 1995). An RCT of 344 infants admitted to the NICU and SCN settings showed significantly fewer blood-culture contaminants in infants having skin disinfection with 1% aqueous CHG compared with those using 10% PI (Nuntnarumit & Sangsuksawang, 2013).

A sequential study reported that the rate of positive blood cultures (the number of true infections or contaminated cultures during the time when 10% PI was used in this NICU) was not statistically different from a subsequent period when 0.5% CHG/IA was used (Linder et al., 1997). A pilot trial of 47 infants who weighed more than 1,500 g and were older than 7 days of age evaluated cutaneous tolerance of 2% CHG/IA compared with 10% PI for PICC placement. There were no differences in the number of bloodstream infections or sepsis evaluations between the two groups; however, this pilot study was not powered to look at bloodstream infection rates (Garland et al., 2009). An RCT of 304 preterm infants compared 2% CHG/IA to 10% PI for insertion of

815 central venous catheters, and reported no difference between the proportion of catheter-related bloodstream infections between the two disinfectants, although more infants in the PI group had thyroid dysfunction. The authors acknowledged that the study was not adequately powered to detect differences in actual numbers of catheter-related bloodstream infections and that a larger study is needed (Kieran et al., 2018).

Toxicity From Skin Disinfectants. If absorbed through the skin, PI has been shown to alter thyroid function in premature newborns. A systematic review of 15 articles reported evidence of thyroid dysfunction in premature infants exposed to iodine-containing disinfectants, with incidence ranging from 12 to 33 cases per 100 infants. The review also found no long-term neurodevelopmental studies that cited harm from exposure to iodine-containing solutions; although the researchers recommended restricting iodine-containing solutions in premature infants, more research is needed (Aitken & Williams, 2014).

Systemic toxicity from percutaneous absorption of CHG in neonates has been raised as a concern. A small study of CHG antisepsis for PICC placement and subsequent dressing changes in premature infants who weighed more than 1,500 g found measurable concentrations of CHG, ranging from 13 to 100 mcg/mL, in 7 of the 10 infants who had levels drawn. However, there were no reported systemic side effects. The role of IA in combination with CHG may be a possible contributing factor to cutaneous absorption of CHG (Garland et al., 2009). Another study involving 20 premature infants with a median gestational age of 28 weeks had an extremity disinfected with 2% aqueous CHG prior to insertion of a PICC. Ten infants had detectable serum CHG levels ranging from 1.6 to 206 mcg/mL, with the highest levels occurring 2 to 3 days after initial exposure (Chapman et al., 2013).

Past reports of neurotoxicity from exposure to hexachlorophene bathing (J. Anderson et al., 1981; CDC, 1973) have prompted research on the potential neurotoxicity from systemic absorption of CHG. An in vitro model of neurite cells was exposed to CHG levels comparable to the highest levels reported in premature infants. CHG inhibited L1-mediated neurite growth and researchers concluded that it is important to determine whether the blood–brain barrier is permeable to CHG in premature infants (Milstone et al., 2014).

There is interest in using CHG to decrease infection in adult and pediatric ICU patients and patients with central venous catheters with daily wiping of skin surfaces with CHG (Milstone et al., 2013). A study was undertaken in a NICU population using 2% CHG–impregnated wipes in a quasi-experimental design, comparing the treated infants to a historical cohort. The algorithm for wiping the skin with CHG determined the frequency based on postnatal age and weight. A decrease in central line–associated bloodstream infections was reported; however, infants weighing less than 1,000 g and younger than 28 days were excluded from CHG bathing. Serum CHG levels were not obtained (Quach et al., 2014).

A number of case reports document chemical burns in premature infants from disinfectants containing CHG; these include various concentrations of CHG, both aqueous and alcohol preparations (Andersen, Hart, Vemgal, & Harrison, 2005; Bringué Espuny et al., 2010; Kutsch & Ottinger, 2014; Lashkari, Chow, & Godambe, 2012; Mannan, Chow, Lissauer, & Godambe, 2007; Neri et al., 2017; Reynolds, Banerjee, & Meek, 2005). There have also been reports of chemical burns from IA and PI solutions in extremely low birth weight infants (Figure 12.7; Sardesai, Kornacka, Walas, & Ramanathan, 2011).

The UK Medicines and Healthcare Products Regulatory Agency published a review of 44 case reports of chemical burns after the application of aqueous or alcohol-based CHG solutions.

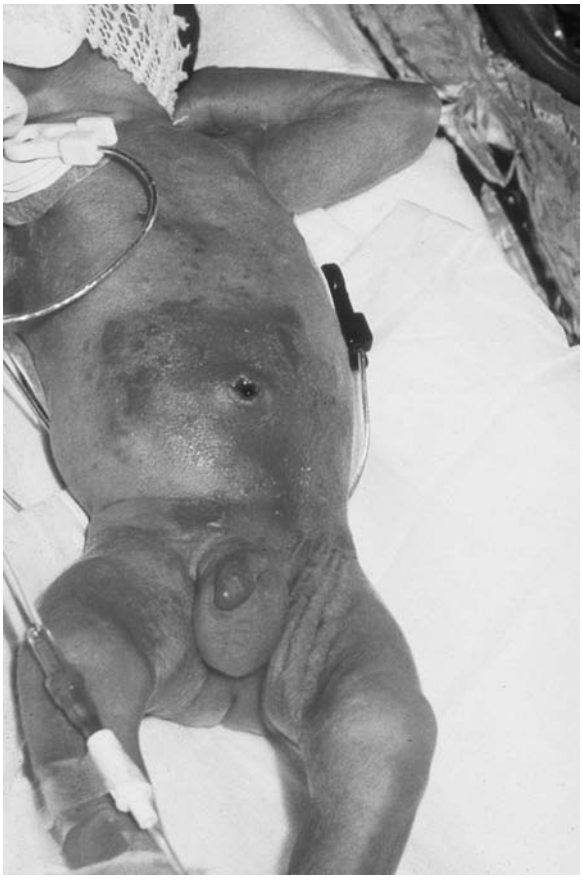


FIGURE 12.7 Skin injury resulting from skin disinfectant.

Most burns occurred in premature infants younger than 26 weeks of gestation or those who weighed less than 1,000 g with long-term sequelae in some infants, to include scarring, discoloration, and keloid formation (Beresford, 2015). Because of these concerns, safety labeling in the United States and Europe continues to state the potential for chemical burns from CHG solutions used for skin disinfection in premature infants (Paternoster, Niola, & Graziano, 2017).

Several studies have been undertaken to determine how CHG affects skin integrity. A prospective study of 40 infants with a mean gestational age of 32 weeks (range 23–39 weeks) found that the use of 2% CHG/IA for PICC insertion and weekly dressing changes compromised skin-barrier function, which was measured by elevated TEWL, an increase in erythema, and dryness (Visscher, deCastro, et al., 2009). A pilot trial comparing 2% CHG/IA in 47 premature infants weighing more than 1,500 g and older than 7 days of age found no increase in skin redness or breakdown when CHG was used for PICC insertion and weekly dressing changes and only one incidence of erythema in a newborn treated with PI (Garland et al., 2009).

The selection of appropriate disinfectants in neonates remains a dilemma, particularly for extremely premature infants during the first weeks of life. CHG products in the United States are limited to a 2% aqueous surgical scrub solution available only in 4-oz bottles and a 2% and 3.15% chlorhexidine solution in 70% isopropyl alcohol available in single-use packaging. The U.S. Food and Drug Administration states that chlorhexidine-containing disinfectants should be used with care in premature infants or infants less than 2 months of age, as these may cause skin irritation and chemical burns. PI continues to be used in many nurseries to avoid

the previous complications, although the issues of thyroid toxicity remain a concern.

Although removal of disinfectants with sterile water or saline after the procedure is complete is advocated (AWHONN, 2018), the manufacturer of the 2% CHG/IA product advises that removal not be attempted, as the residual effect of the disinfectant on the skin may be beneficial. However, it is not known whether this feature may contribute to skin irritancy and absorption of CHG in newborns and premature infants.

CHG should not be used as preoperative skin disinfection on the face or head because misuse has been reported to result in injury if it remains in contact with either the eye or ear during surgical procedures. However, careful use before scalp intravenous or central-line insertion is acceptable, providing that splashing or using excessive amounts of chlorhexidine is avoided. In addition, there is no clinical data to discourage the use of chlorhexidine gluconate products prior to lumbar puncture or epidural catheter placement, as this is considered skin antisepsis (Milstone, Passaretti, & Perl, 2008).

Umbilical Cord Care

The use of antibiotic ointments and skin antiseptics to the umbilical cord can prolong the time to cord separation and has no beneficial effect on the frequency of infection (Zupan & Garner, 2000). Although the umbilicus is a possible route for infection by invasive pathogenic microorganisms until healed, the evidence suggests that dry cord care, defined as keeping the cord clean and leaving it exposed to air or loosely covered by a clean cloth, is effective for infants born in high-resource countries (Stewart, Benitz, & Committee on Fetus and Newborn, 2016).

For newborns born in health facilities, dry cord care is recommended, as there are a number of studies to support this practice. A cluster randomized controlled trial in France, involving over 8,000 near-term and term newborns, found dry cord care was not inferior to antiseptic cord care in preventing omphalitis (Gras-Le Guen et al., 2017). A group of 150 consecutively born, healthy, late preterm and term infants born in a hospital setting in Taiwan (high humidity, subtropical country) was randomized to alcohol or dry cord care. Cord separation time was significantly decreased for those infants having dry cord care compared with those cleansed with 95% isopropyl alcohol, and the incidence of cord infection was not increased (Hsu et al., 2010). A meta-analysis showed the use of topical isopropyl alcohol was not superior to dry cord care in reducing the incidence of omphalitis (Imdad et al., 2013).

Medical Adhesives

Hospitalized full-term and premature newborns require the routine use of adhesives to secure life support and monitoring equipment such as endotracheal tubes, intravenous devices, oxygen saturation sensors, and electrodes. The types of medical adhesives used in the NICU are categorized as acrylates, hydrocolloids, hydrogels, and silicone-based adhesives (Lund, 2014).

Acrylate-based adhesives include products such as paper, plastic, and soft cloth tape. These types of adhesives have increased adherence over time and may leave a residue on the skin after removal (McNichol, Lund, Rosen, & Gray, 2013). However, acrylate adhesives adhere effectively to skin and medical devices and are commonly used in intensive care settings. Polyurethane films with acrylate adhesives such as transparent adhesive dressings allow visualization of catheter insertion sites and are permeable to water vapor, oxygen, and carbon dioxide, allowing the skin to breathe (Darmstadt & Dinulos, 2000).

Hydrocolloid adhesives were initially used to protect peristomal skin for ostomy patients and later became a wound dressing. They are sometimes used as a platform between skin and tape and are sometimes integrated into some products such as an endotracheal tube securement device. Initially hoped to be gentler on the skin when removed, hydrocolloids have been shown to cause skin trauma equal to acrylate tape when removed at 24 hours (Lund et al., 1997). Other studies have also reported decreased skin-barrier function, measured by increased TEWL and erythema, under hydrocolloids (Zillmer, Agren, Gottrup, & Karlsmark, 2006). However, these barriers are still used because they absorb moisture, mold well to skin surfaces, and, as noted previously, serve as a platform between skin and acrylate tapes and transparent dressings (Boswell & Waker, 2016; Cheng & Kroshinsky, 2011; O'Neil & Schumacher, 2014). One study found no statistically significant quantitative difference between a transparent dressing placed over a hydrocolloid base or a transparent dressing placed directly on the skin. Despite this lack of support for one method over the other, they found a theme of comments from nurses that they preferred transparent dressings placed over a hydrocolloid base as a more effective adhesive and a belief that it was gentle for the skin (Boswell & Waker, 2016).

Hydrogels are a low-trauma and highly breathable adhesive with high water content. Hydrogels are found in some adhesive products such as EKG electrodes and temperature probe covers; they are also available as tapes for securement of tubes. Hydrogels are also available as a dressing for wounds and may have a cooling or analgesic effect on wounds. Use of hydrogel adhesives has been shown to reduce the trauma associated with electrode removal (Darmstadt & Dinulos, 2000; Lund et al., 1997; Webster & McCosker, 1994). However, they do not adhere well enough to secure critical lines and tubes and do not function well in high humidity environments such as humidified incubators.

Silicone-based adhesive products have been shown to improve adherence to skin and reduce discomfort to patients with adhesive removal. This technology holds promise for developing products that adhere and cause minimal trauma such as erythema, skin stripping, and keratin loss, compared with acrylate-based paper tapes when removed from the skin of pediatric patients (Grove, Zerweck, Ekholm, Smith, & Koski, 2014). However, silicone adhesives do not adhere well to plastic devices, such as nasogastric tubes and cannulas, which may limit their use for attaching some medical devices. A beneficial use of silicone adhesives is as a border for dressings, which can be lifted up and replaced for wound assessment. Another application for silicone adhesives is for securing brain-monitoring electrodes, as they adhere well to hair and can be removed with minimal discomfort.

Newborns are at high risk for medical adhesive-related skin injury (MARSI), a term first used in a consensus paper involving a number of different health providers representing several specialties including pediatrics, gerontology, orthopedics, and dermatology and wound care experts (McNichol et al., 2013). Types of MARSI include skin stripping, skin tears, contact, and allergic dermatitis.

Newborns are particularly vulnerable to MARSI; the evidence-based practice project for the Neonatal Skin Care Guideline, which included skin and environment assessments for 2,820 premature and full-term newborns, found that adhesives were the primary cause of skin breakdown (Lund et al., 2001). It is known that functional changes in adult skin, including altered skin barrier function (measured as increases in TEWL), are seen after 10 consecutive applications and removals of adhesive tape (Lo, Oriba, Maibach, & Bailin, 1990), and after one application/removal in premature infants (Harpin & Rutter, 1983; Lund et al., 1997).

Liquid skin-barrier films are skin protectants wiped on the skin prior to attaching adhesives and have been shown to protect the

skin from adhesives as well as fecal and ostomy output and urine (Black, 2007). Silicone-based skin barrier films do not sting when applied, rapidly evaporate, and do not leave a residue in addition to the general benefits of silicone-based skin protectants in neonates (Irving, 2001). A study of premature infants (<33 weeks) showed both skin protection and the additional benefit of reduced TEWL (Brandon, Coe, Hudson-Barr, Oliver, & Landerman, 2010). Although this study found efficacy without any safety concerns, additional research is warranted in a larger ELBW population.

Removal of medical adhesives can cause trauma, such as skin stripping and pain. **Quality and Safety: A technique involving slowly pulling adhesives at a very low angle, parallel to the skin surface, while holding the surrounding skin in place, may reduce epidermal stripping** (Lund & Tucker, 2003; McNichol et al., 2013). Adhesive removers help to aid in the atraumatic removal of adhesives. There are three categories of adhesive removers: alcohol–organic-based solvents, oil-based solvents, and silicone-based removers (Black, 2007; Cooper, 2010). Solvents contain hydrocarbon derivatives, petrolatum distillates, or isopropyl alcohol, and carry the potential of systemic and topical toxicities. A case report of a premature infant developing a severe dermatologic reaction to an adhesive remover, including blistering and hemorrhage, suggest the lack of safety with these products in a NICU (Ittmann & Bozynski, 1993). Oil-based solvents release the bond between skin and adhesive and are based on paraffin or citrus oil extracts. These do not evaporate and leave a residue that prevents adherence during reapplication of adhesives to the site where they were previously applied.

Silicone-based removers form an interposing layer between adhesive and skin, allowing for easier removal. These evaporate readily after application without drying of the skin and are less likely to leave a residue. They do not cause stinging, even on broken skin; and are inert, reducing the risk of toxicity. Silicone-based removers are available in spray, liquid, lotion, or wipe formulations (Cooper, 2010). Researchers have demonstrated the safety and effectiveness of using silicone-based removers in the neonatal population, including infants with epidermolysis bullosa (Cooper, Russell, Stringfellow, Duguid, & Pirie, 2011; Denyer, 2011).

Transepidermal Water Loss

Because of the poorly keratinized *stratum corneum* that provides minimal resistance to the diffusion of water, the preterm infant is at risk for TEWL through the skin, and heat loss via evaporation. Characteristic skin factors that predispose premature infants to excessive water loss include reduced skin barrier function from fewer layers of *stratum corneum* and thinner epidermis, larger surface area in relation to body weight, increased water content, increased permeability, and increased blood supply closer to the skin surface. Mature keratin, a major component of the tough, nonliving outer layer of the epidermis, is relatively water-impermeable. Because keratin formation is directly related to gestational age, the premature infant less than 30 weeks' gestation is at increased risk for increased TEWL and evaporative heat loss.

Premature infants of 23 to 25 weeks' gestation have TEWL that is 10 times higher than full-term newborns (Agren et al., 1998; Visscher et al., 2015). Mature barrier function—at one time thought to advance rapidly over a 2-week period in premature infants less than 30 weeks' gestation—has been shown to take longer in extremely premature infants of 23 to 24 weeks' gestation and occurs when the infant reaches approximately 30 to 31 weeks postconception age (Kalia et al., 1998).

In the delivery room, premature infants less than 28 weeks' gestation are placed in a polyethylene bag or wrap without drying the skin, in an effort to reduce the degree of evaporative heat loss and hypothermia/cold stress during initial stabilization (Bissinger & Annibale, 2010; Knobel, Wimmer, & Holbert, 2005; Vohra, Roberts, Zhang, Janes, & Schmidt, 2004). This technique is so effective that studies have reported hyperthermia in some infants; thus, careful monitoring of temperature is needed.

High humidity, a relative humidity (RH) greater than 70%, added to an incubator has been shown to effectively reduce evaporative heat loss and TEWL; the rate of TEWL has been shown to decrease by half when the RH increases from 20% to 60% (Hammarlund & Sedin, 1979; Harpin & Rutter, 1983). The use of humidified "hybrid" incubators in premature infants less than 1,000 g are capable of providing high humidity in a convectively heated incubator and also radiant heat for procedures and emergencies. A study reported positive effects on fluid balance, electrolyte stability, and growth velocity after the hybrid humidity devices were implemented, compared to a historical control group (Kim, Lee, Chen, & Ringer, 2010). This study utilized high levels of humidity (70%–80%) for the first week, with reduced humidity levels to 50% to 60% for the second week until the infant reached 30 to 32 weeks postconception age (Kim et al., 2010). The rationale for reducing the humidity level in this fashion was based on an earlier RCT that demonstrated improved skin barrier function and maturity when humidity levels were reduced to 50% compared to 75% in the second week of life (Agren et al., 2006).

FIGURE 12.8 Silicone-based adhesives developed for use in wound care products are now available as silicone tapes and have been shown to improve adherence to wounds and reduce discomfort when removed.

Application of petrolatum-based emollients every 6 to 12 hours also reduces TEWL and can be used on infants on radiant warmers or under phototherapy without temperature increases or burns (Nopper et al., 1996). A novel use of a protective barrier film was also shown to reduce TEWL compared to petrolatum ointment in premature infants less than 33 weeks' gestation (Brandon et al., 2010). However, due to the concerns raised in a large RCT of infants less than 1,000 g regarding increased coagulase negative staphylococcus infections with prophylactic use of this petrolatum ointment. These approaches are not recommended without further study.

Because of the numerous benefits of skin-to-skin holding (kangaroo care), a study was undertaken to measure evaporative loss while out of the high humidity environment. Five premature infants of 22 to 26 weeks' gestation were held skin-to-skin by their mothers at 3 to 9 days of age; covering with a single layer of cotton fabric resulted in decreased evaporative heat loss (Kjällström, Sedin, & Ågren, 2011).

Thus, addressing the important area of reducing excessive heat loss and TEWL is necessary in the care of the extremely premature neonates to maintain adequate hydration without excessive fluid intake. The goal of maintaining hydration and normal serum sodium levels on an intake of less than 150 mL/kg/day is optimal and achievable using preventive strategies.

MANAGEMENT OF SKIN CARE PROBLEMS

The *stratum corneum* can be traumatized by a variety of insults, including epidermal stripping from removal of adhesives; chemical burns from disinfectants; pressure injuries, especially from medical devices; infection; nutritional inadequacies, such as zinc and essential fatty acid deficiency; extravasation of intravenous fluids; and diaper dermatitis. The goal of all skin care for neonates should be the maintenance of skin integrity; however, even with meticulous care, skin breakdown can occur.

Skin Assessment

A thorough examination of all skin surfaces on a daily basis will reveal the state of skin integrity in critically ill or extremely premature infants in the NICU. Early signs of skin abrasions or small excoriations may call for either diagnostic or treatment procedures. A skin assessment tool such as the Neonatal Skin Condition Score (NSCS; Box 12.1; Figure 12.9), used in the AWHONN/National Association of Neonatal Nurses (NANN) research-based practice project, may be beneficial when assessing skin conditions (Lund et al., 2001). The NSCS was found to have both interrater and intrarater reliability, and validity was confirmed by the relationship of the skin scores with birth weight, number of observations over time, and prevalence of infection (Lund & Osborne, 2004). Identifying risk factors for skin injury in individual patients may include gestational age less than 32 weeks, use of paralytic medications and vasopressors, multiple tubes and lines, numerous monitors and probes, surgical wounds, ostomies, and technologies that limit patient

Box 12.1

NEONATAL SKIN CONDITION SCORE

Dryness

1 = Normal, no sign of dry skin
2 = Dry skin, visible scaling
3 = Very dry skin, cracking/fissures

Erythema

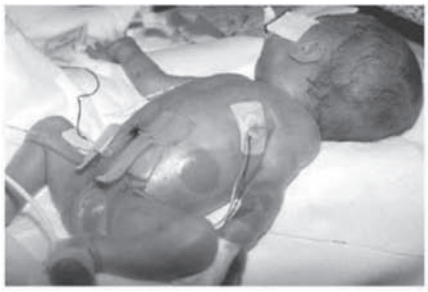
1 = No evidence of erythema
2 = Visible erythema over <50% of the body's surface
3 = Visible erythema on >50% of the body's surface

Breakdown/Excoriation

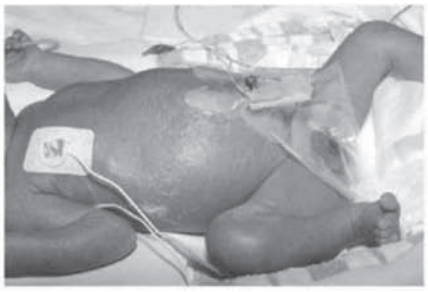
1 = None evident
2 = Small localized areas
3 = Extensive

Note: Perfect score = 3; worst score = 9

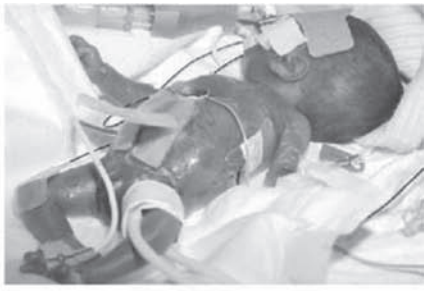
Source: Adapted from Lund, C. H., Osborne, J. W., Kuller, J., Lane, A. T., Lott, J. W., & Raines, D. A. (2001). Neonatal skin care: Clinical outcomes of the AWHONN/NANN evidence-based clinical practice guideline. Association of Women's Health, Obstetric and Neonatal Nurses and the National Association of Neonatal Nurses. *Journal of Obstetrics, Gynecology, and Neonatal Nursing, 30*(1), 41–51. doi:10.1111/j.1552-6909.2001.tb01520.x. Copyright © 2001, AWHONN.



Dryness: 1 = normal, no sign of dry skin
Erythema: 2 = visible erythema <50% body surface
Breakdown: 3 = extensive



Dryness: 2 = dry skin, visible scaling
Erythema: 1 = no evidence of erythema
Breakdown: 1 = none evident



Dryness: 2 = dry skin, visible scaling
Erythema: 3 = visible erythema >50% body surface
Breakdown: 3 = extensive

FIGURE 12.9 Examples of skin assessments in three infants using the Neonatal Skin Condition Score (NSCS).

movement such as high-frequency ventilation and extracorporeal membrane oxygenation.

Other scoring tools such as the Braden Q and Starkid Scale that assess risk for pressure sores have been suggested (Curley, Razmus, Roberts, & Wypij, 2003; Suddaby, Barnett, & Facteau, 2005). However, in these studies the number of neonates is not indicated, patients from ages 0 to 12 months are evaluated as a single group, and no premature infants were included so the applicability of these tools to a NICU population has not been demonstrated.

The Braden QD was developed to predict hospital-acquired pressure injuries (HAPI) in pediatric patients, including those caused by both immobility and medical devices. Their study involved 625 patients, with 17% less than 1 month of age. The overall HAPI rate was lower than expected, with 86 HAPI found in 49 patients; 75% were device-related (Curley et al., 2018).

The Braden QD evaluates for intensity and duration of pressure in terms of the patient's mobility and sensory perception. It also evaluates skin tolerance in terms of friction, shear, nutrition, tissue perfusion, and oxygenation. In addition, the number of medical devices is quantified as well as the ability to reposition devices and sensors. However, there is no scoring for prematurity or gestational age, both important aspects of skin tolerance in NICU patients, so how helpful the use of the Braden QD in NICU patients is remains questionable. It is also important to recognize that risk assessment is not the same as skin assessment and careful observation and documentation of the skin condition are essential components of skin care in NICU patients.

Skin Injuries

Although little clinical research is available to guide selection of topical agents and products to treat skin injuries in neonates, there are several principles to help inform practitioners. These include the concept of moist wound healing, gentle cleansing, and understanding the proper application of appropriate dressings (Cousins, 2014; M. D. Fox, 2011). In addition, although the injury may be due to mechanical trauma, the role of microorganisms can further complicate the management of skin injury, especially in the very low birth weight premature infant. In these cases, a skin culture may be helpful.

If the culture is positive for a candidiasis species, antifungal ointment and systemic treatment with fluconazole or amphotericin may prevent devastating, disseminated disease (Benjamin et al., 2010; Darmstadt, Dinulos, & Miller, 2000). Although fungal causes are sometimes suspected, other microorganisms such as *S. aureus* species, *Escherichia coli,* and other gram-negative bacteria have also been cultured in extremely premature infants. The knowledge of their skin colonization may be very useful in guiding systemic treatment should their clinical condition worsen, suggesting systemic disease, including sepsis.

Ointments are sometimes used on skin injuries not only because of their antibacterial or antifungal properties but also because covering the wound with a semi-occlusive layer promotes healing by facilitating the migration of epithelial cells across the surface. Petrolatum-based emollients and ointments are used to cover wounds and provide a semi-occlusive layer that facilitates the migration of epithelial cells across the surface and may actually become part of the *stratum corneum* layer during the healing process. Antibacterial ointments such as Polysporin, Bacitracin, or Bactroban are useful to treat gram-positive colonized surfaces but also actually promote the growth of gram-negative organisms (Smack et al., 1996). Many dermatologists recommend against the use of Neosporin because of the potential for developing later sensitization to this ointment, although sensitization to Bacitracin is being reported with increasing frequency (Marks et al., 1995). If fungal infection is suspected, nystatin ointment is used and can also be applied to surrounding intact skin to prevent extension of the infection. In general, ointments are preferable to creams in this application because of better adherence and healing properties.

Gentle cleansing of the skin injury or wound can remove debris and exudate and promote a clean wound bed. These materials and other necrotic tissue impede wound healing and the removal reduces the level of bacterial contamination (Cousins, 2014). Wound cleansing is best accomplished by gentle irrigation with normal saline, either diluted or undiluted, using a 20 to 60 mL syringe and a blunt intravenous catheter (AWHONN, 2018). Antiseptic solutions and cleansers are to be avoided as these can cause further injury to delicate healing tissue and may delay healing (Lineaweaver et al., 1985; Rolstad & Ovington, 2007; Wilson, Mills, Prather, & Dimitrijevich, 2005).

Dressings for wound care and for treating skin injury should be occlusive and nonadherent in order to promote moist healing to facilitate the migration of epithelial cells. These include silicone dressings, hydrocolloid dressings, hydrogel dressings, transparent dressings, and dressings made of foam or other composite materials. In addition, some may be impregnated with silver ions, with potential benefit due to anti-infective properties (M. D. Fox, 2011). Although use of silver-containing creams and dressings were initially avoided due to concerns with toxicity, more recent articles demonstrate safe uses of silver-containing agents in neonates (August, Ireland, & Benton, 2015; Tenenhaus, Greenberg, & Potenza, 2014).

Medical grade honey, either as an ointment or in a dressing, has also been described for use in neonates and may also be used to facilitate debridement (Amaya, 2015). Benefits include anti-infective properties and facilitating moist healing cascade (Alvarez-Suarez, Gasparini, Forbes-Hernández, Mazzoni, & Giempieri, 2014). There are several case studies that report positive results using medical grade honey in premature infants (Boyar, Handa, Clemens, & Shimborske, 2014; Esser, 2017; Mohr, Reyna, & Amaya, 2014).

Intravenous Extravasations

The extravasation of intravenous fluids and medications can result in skin injury and, in some cases, deep-tissue injury to muscle and nerves (Figure 12.10). Neonates are at high risk for developing extravasation injuries because of their immature skin, lack of subcutaneous tissue, and the small size of their blood vessels (Amjad, Murphy, Nylander-Housholder, & Ranft, 2011; Casanova,

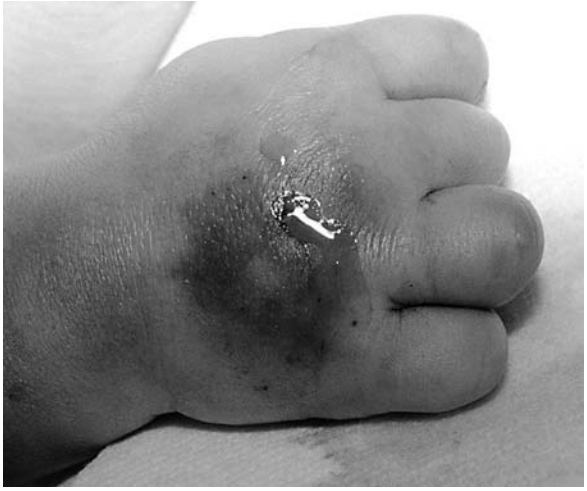


FIGURE 12.10 Intravenous extravasation injury with swelling, discoloration, and leaking of fluid.

Bardot, & Magalon, 2001). The most serious extravasation injuries are iatrogenic complications that can lead to pain, prolonged hospitalization, and increased morbidity, such as infection. Extravasation injuries can also result in increased hospital costs and the potential for legal action.

Nursing actions such as the monitoring of intravenous sites and other preventive strategies as well as immediate interventions that reduce the extent of tissue injury are important considerations for all nurseries that care for newborns with intravenous devices for fluid administration and medications. Some of the risk factors for tissue injury from intravenous extravasations in NICU patients are listed in Box 12.2.

Hourly assessments of insertion site, with more frequent assessments during administration of certain medications, is recommended, as well as not relying on the infusion pump to detect infiltration of fluid into the tissue (Amjad et al., 2011; Simona, 2012; Tofani et al., 2012). Quality improvement efforts involving standardizing assessment strategies have been described and are beneficial, such as "Touch, Look, Compare" and "Assess, Compare, Touch" (Tofani et al., 2012; Wilder, Kuehn, & Moore, 2014). One center included these aspects of assessment, along with review of factors such as catheter type, securement method, and daily review of catheter necessity; these efforts resulted in a reduction in infiltration rates over a 6-month period (Watterson et al., 2018).

Prevention of skin injury after infiltration is an important consideration. Strategies include ensuring that the insertion site is clearly visible by using transparent adhesive dressing or clear tape to secure the device and observing the site with appropriate documentation every hour. In addition, the tape should be carefully placed on the extremity to avoid obstruction of venous return. Tape placed loosely over a bony prominence, such as the knee or elbow, permits extravasated fluids and medications to disperse over a larger surface area and thus reduce the risk of injury, compared with extravasation limited to a small surface area. Avoiding extremities with poor perfusion in favor of better-perfused scalp veins (except, of course, those on the forehead) may also be prudent; in some cases, the wiser choice may be the placement of central venous lines for access.

The fluid that is being infused is a known factor that can lead to greater risk of extravasation. The risk is related to the fluid's chemical properties, osmolality, and pH (Gorski et al., 2017). Normal serum osmolality is 280 to 295 mOsm/kg and solutions that exceed this are considered hypertonic. Solutions that are infusing through a peripheral vein in a neonate should stay within this range (Thigpen, 2007). Glucose concentrations that are higher than 12.5% are at risk for extravasation injury (Weinstein, 2007).

Medications can be both hyperosmolar and irritating due to pH extremes. Particularly irritating medications and solutions, called vesicants, should be either avoided or carefully watched during infusion. A chart showing various degrees of vesicants can be a helpful guide for neonatal patients and may also identify patients who would benefit from central venous access (Gorski et al., 2017).

Once an intravenous extravasation has been identified, immediate measures to reduce injury are instituted (Thigpen, 2007). The device should be carefully removed and the extremity elevated (if it is an arm or leg). Treatment with heat or moisture is not recommended because the delicate tissue could be further injured by a burn or the effects of maceration. Making multiple puncture holes over the area of greatest swelling and squeezing to allow the fluid to leak out of the tissue releases the infiltrated fluid and can potentially prevent skin injury (Chandavasu, Garrow, Valda, Alsheikh, & Dela Vega, 1986; Sawatzky-Dickson & Bodnaryk, 2006). Saline washout has also been described (Casanova et al., 2001; Davies, Gault, & Buchdahl, 1994; Kostogloudis et al., 2015), although no randomized trial has been published to compare efficacy (Gopalakrishnan, Goel, & Banerjee, 2017).

Hyaluronidase is an enzyme that facilitates diffusion of the extravasated fluids by temporarily dissolving the normal interstitial barriers, reducing tissue damage, and has been reported to reduce tissue injury following extravasation in neonates (Banta & Noerr, 1992; Laurie, Wilson, Kernahan, Bauer, & Vistnes, 1984; Raszka, Kueser, Smith, & Bass, 1990). A dose of 15 to 20 U is administered in five subcutaneous injections around the periphery of the extravasation (Treadwell, 2012), and this dose may be repeated. The addition of multiple punctures may also facilitate flow of fluid from the tissues, as well as keeping the site moist for several hours using hydrogel products or moist compresses.

If tissue damage results despite the immediate care measures, the use of topical wound care treatments is necessary. In the most severe cases of deep-tissue necrosis after extravasation injury, a surgical or plastic surgery consultation may be necessary (Figure 12.11).

Diaper Dermatitis

A common skin disruption that occurs in neonates and infants is diaper dermatitis (diaper rash). This term encompasses a range of processes that affect the perineum, groin, thighs, buttocks, and anal area of infants who are incontinent and wear some covering to collect urine and feces. Diaper dermatitis can be caused by

Box 12.2

RISKS FOR TISSUE INJURY FROM INTRAVENOUS EXTRAVASATIONS

Some of the factors known to increase the risk of tissue injury include:

- The length of exposure after extravasation occurs, especially when the patients are unable to verbalize the discomfort of pain or pressure
- The nature of the drug or solution; hypertonic solutions with high concentrations of calcium, potassium, glucose, or amino acids; and medications such as nafcillin have been identified as high risk for causing injury
- The mechanical compression caused by electronic infusion pumps

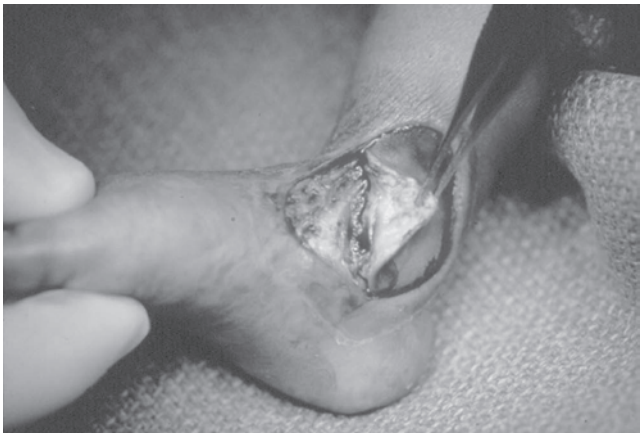


FIGURE 12.11 This intravenous extravasation injury will require plastic surgery.

many different mechanisms, but the condition of the skin has a direct role in the progression of skin injury. Review articles provide an excellent background for current evidence-based care in the prevention and treatment for diaper dermatitis (Adam, 2008; Heimall, Storey, Stellar, & Davis, 2012).

The pathogenesis of diaper dermatitis is partly related to the degree of wetness of the skin. Skin that is moist and macerated becomes more permeable and susceptible to injury because wetness increases friction. In addition, moisture-laden skin is more likely to contain microorganisms than dry skin.

Another component in the process of skin injury from diaper dermatitis is the effect of an alkaline pH. The normal skin pH is acidic—ranging between 4.0 and 5.5—but can become alkaline when it is diapered (Visscher, Chatterjee, Ebel, LaRuffa, & Hoath, 2002; Visscher, Chatterjee, Munson, Pickens, & Hoath, 2000). It is the resulting increased pH of the skin that increases its vulnerability to injury and penetration by microorganisms. Another problem associated with increased pH of the skin is that it stimulates fecal enzyme activity. Specifically, both protease and lipase, which are found in stools, can injure the skin, which is made up of protein and fat components. These enzymes can cause significant injury to the epidermis fairly quickly and are responsible for the contact irritant diaper dermatitis that is commonly seen.

Once the epidermis has been impaired or becomes a less efficient barrier because of one of the aforementioned mechanisms, invasion by bacteria or fungus can occur. Thus, a contact irritant diaper dermatitis can turn into a staphylococcal or fungal rash if this progression occurs. *S. aureus* can be found in large numbers on the skin surface, especially if it is inflamed or impaired, and can result in secondary infection. The classic presentation for *S. aureus* is pustule formation at the site of hair follicles, although the overall incidence of *S. aureus*-complicated diaper dermatitis is quite low.

Fungal rashes, primarily those caused by *C. albicans*, may have different mechanisms of invasion. Many researchers have identified *C. albicans* as a secondary invader of skin that has been injured by other mechanisms, whereas others suggest that *C. albicans* is a primary causative factor in diaper dermatitis. This theory is based on the ability of *C. albicans* to penetrate the *stratum corneum*, especially in a warm and moist environment, such as that found under an occlusive diaper. The resulting intense inflammation is significant and appears as brightly erythematous, sharply marginated dermatitis that involves the inguinal folds as well as the buttocks, thighs, abdomen, and genitalia, characteristically with satellite lesions that may extend the rash over the trunk (Figure 12.12). The gastrointestinal tract is often the reservoir for *C. albicans*, and it can frequently be recovered in stools. Oral therapy may be indicated, especially if evidence of oral infection, such as thrush, is apparent.

Diaper dermatitis can be the result of a primary dermatological condition, such as psoriasis, eczema, and seborrheic dermatitis. Significant family history of these skin conditions may identify infants who are especially vulnerable to developing severe reactions to inflammation in the diaper area. The role of allergens has also been implicated in some cases of diaper dermatitis and should be considered when treatment strategies fail (Smith & Jacob, 2009).

Management

Prevention is the first goal of intervention and is paramount in breaking the cycle of diaper dermatitis. Frequent diaper changes result in skin that is drier with a more normal pH and a more normal functional barrier of the skin. Strategies to keep the skin dry also include the use of highly absorbent gelled diapers that act to "wick" moisture away from the skin. Use of baby powders is discouraged because of the risk of inhalation of particles into the respiratory tract.

The use of commercially available diaper wipes, although in widespread use, has variable support in the literature with reports of contact allergens and concerns with product ingredients (Ehretsmann, Schaefer, & Adam, 2001; Fields, Nelson, & Powell, 2006; Smith & Jacob, 2009). A carefully controlled study of one brand of wipes compared to cloth and water for skin cleansing in the diaper area of premature infants showed improved skin pH and TEWL with the diaper wipe (Visscher, Odio, et al., 2009). An RCT comparing using diaper wipes to cotton balls and warm water found no difference in skin barrier function and changes in skin pH between the two techniques (Lavender et al., 2013). However, these findings are not generalizable to other products with different formulations.

Once diaper dermatitis occurs—and it is not completely avoidable in most infants—protection of injured skin during healing is the primary goal. Use of a generous layer of protective skin barriers that contain petrolatum ointment and/or zinc oxide prevents further trauma and allows impaired skin to heal (Figure 12.13). Although various amounts of zinc are found in different products, there is no evidence that one is better than another (Stamatas & Tierney, 2014). Other ingredients that have been reportedly as beneficial include products with carboxymethylcellulose that adhere extremely well to excoriated skin (Esser, 2016). The ingredient cyanoacrylate, found in "liquid bandages," is now found in some products for incontinence-associated dermatitis in adults and hold

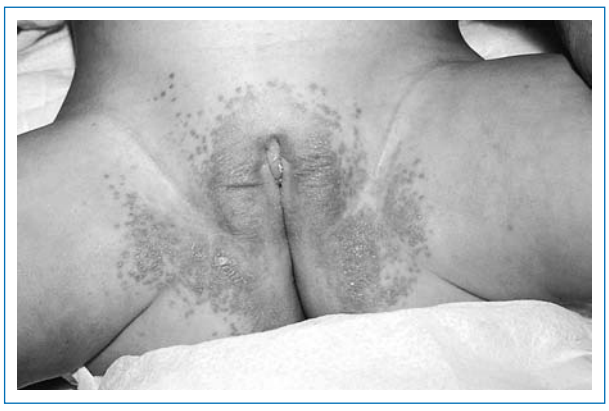


FIGURE 12.12 Candida diaper dermatitis involving labia and inguinal folds with characteristic satellite lesions.

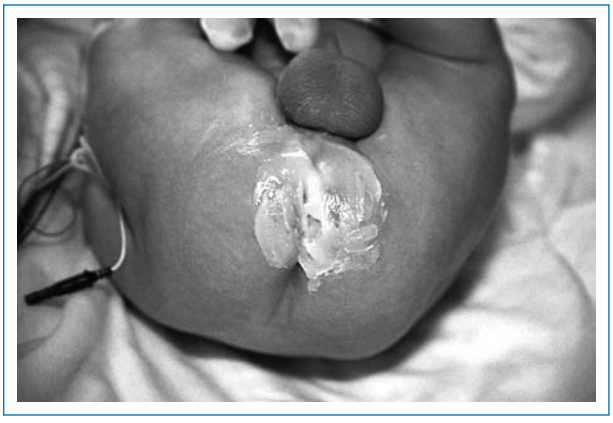


FIGURE 12.13 Use of thick layer of a skin barrier such as zinc oxide or pectin paste will prevent reinjury of skin damage in diaper dermatitis.

promise for the most severe cases of diaper dermatitis in infants and children (Brennan, Milne, Agrell-Kahn, & Ekholm, 2017).

Opening the skin to light and air is not effective if the fecal contents are allowed to have direct contact with already injured areas. Because protective skin barriers tend to adhere well to the skin, it is neither necessary nor desirable to completely remove them during diaper changes before more cream is applied because the friction that is generated will injure healing tissue. It is best to generously apply more cream to the site to protect the area from further injury.

Multiple products are used in the care of diaper dermatitis—including topical emollients, diaper rash balms, and wipes—but product selection is often affected by myth and tradition rather than science. A damp diaper covered with a plastic coating enhances the risk of irritation and percutaneous absorption. The risk of absorption is even greater in newborns and premature infants because of their large surface area to body weight ratio and immature skin. The various compounds and numerous chemicals used have been described extensively (Gilliam & Williams, 2008; Siegfried & Shah, 1999), with concerns raised about potential toxicity, irritancy, and later sensitization. Simple, inexpensive products such as zinc oxide ointment are recommended over more complex compounds.

Treatment of diaper dermatitis that is solely due to invasion with *C. albicans* requires the use of antifungal creams or ointments. Some of the antifungal preparations include nystatin, miconazole, and clotrimazole. If the diaper dermatitis involves both fungus and a contact irritant component, alternating applications of the topical creams or ointments is effective.

Severe diaper dermatitis with deep excoriations can be seen in infants with malabsorption syndrome, secondary to intestinal resection or mucosal injury. In these cases, the stool is extremely caustic and contains a higher level of enzyme activity, a lower pH as the result of rapid transit through the intestine, and significant amounts of undigested carbohydrates. In the case of opiate withdrawal, stool frequency is often greatly increased. Other infants at risk for severe diaper dermatitis include those with spina bifida, exstrophy of the bladder, and infants with decreased anal sphincter tone due to early pull-through procedures for Hirschsprung's disease. In cases of loss of sphincter tone, fecal material constantly dribbles to the perianal area.

Although skin disruption frequently becomes the focus of nursing interventions, this symptom may be a significant indication of more serious physiological concerns. These infants' stools should be carefully monitored by documentation of number and volume. The infants must be observed for the dehydration caused by extensive water losses in diarrhea. Once dietary manipulations and hydration have stabilized the general physiologic status, a program of skin protection is imperative because some level of chronic diarrhea may be ongoing for many weeks or months. Products such as pectin-based powders or pectin-containing pastes without alcohol may be better barriers to the caustic, constant fecal irritation if traditional zinc oxide creams do not work adequately. If yeast is present, antifungal creams may be applied in conjunction with protective barriers.

EVIDENCE-BASED SKIN CARE GUIDELINE

Many intensive care and newborn nurseries have written protocols for various aspects of neonatal skin care. The AWHONN and the NANN collaborated in the development of a comprehensive, evidence-based neonatal skin care guideline. An extensive review of the scientific basis for neonatal skin care was undertaken by a team, including advanced practice nurses and a pediatric dermatologist (Lund, Kuller, Lane, Lott, & Raines, 1999), and a neonatal skin guideline was written to address 13 aspects of skin care (Box 12.3). An evaluation project involving 51 nurseries was undertaken to evaluate the effect of using this guideline. The project involved identifying coordinators at each site who were willing to collect baseline information about the skin condition of infants in their units, implement the practice guideline in their respective units, and then collect skin condition information again once the guideline had been introduced. Issues of safety and feasibility were important, as was the evaluation of the impact of evidence-based practice on skin condition.

More than 11,000 skin observations using the NSCS were performed on 2,820 newborns of varying gestational ages and weights. An improvement in skin condition was observed after implementation of the guideline, as evidenced by overall lower scores on the NSCS during the observation period. Initial scores were similar in both the pre-guideline and post-guideline groups but improved more rapidly after the guideline had been implemented. The results were more dramatic in low birth weight infants, but improvement was seen in the "well-baby" sample as well.

The Neonatal Skin Care Guideline was revised in 2007, with the addition of a section on *vernix caseosa* due to the availability of numerous studies published on this topic. A third revision was released in 2013 and a fourth in 2018.

Box 12.3

ELEMENTS OF THE AWHONN/NANN EVIDENCE-BASED PRACTICE GUIDELINE: NEONATAL SKIN CARE

1. Newborn skin assessment
2. Neonatal skin injury
3. Bathing
4. Vernix caseosa
5. Umbilical cord care
6. Diaper dermatitis and diaper wipes
7. Circumcision care
8. Emollient use for dry skin and atopic dermatitis
9. Skin disinfectants
10. Medical adhesives
11. Intravenous extravasation
12. Transepidermal water loss in premature infants
13. Parent education

Source: Adapted from the Association of Women's Health, Obstetric, and Neonatal Nurses. (2018). *Evidence-based clinical practice guideline: Neonatal skin care* (4th ed.). Washington, DC: Author.

SUMMARY

Neonatal skin management is a complex problem that requires a collaborative approach. Some research has been conducted in this area but a lot remains to be done regarding the use of routine NICU equipment and its impact on neonatal skin, the use of skin barriers for protection, and the effect of a consistent approach to skin care on the integrity of neonatal skin. This chapter has outlined the development and structure of the skin. It has addressed differences in the skin based on gestational age variations. Normal physiological as well as common dermatological abnormalities have been presented. Evidence-based neonatal skin care is recommended and has proven to be feasible and safe and to result in improvement in skin condition for newborns.

CASE STUDY

■ **Identification of the Problem.** This extremely premature infant was admitted to the NICU 3 days ago with respiratory distress syndrome; birth weight 650 g, gestational age 24 0/7 weeks. He has an endotracheal tube and is receiving assisted ventilation; catheters are inserted in both the umbilical artery and vein for blood sampling, blood pressure monitoring, and administration of IV fluids. An area of skin breakdown is noted on the abdomen where a temperature probe had been placed and removed on the first day of life. By day 3, the area is erythematous and oozing a yellow-tinged fluid. Surrounding areas are also quite red.

■ **Assessment: History and Physical Examination.** The infant, a baby boy, was born via vaginal delivery to a 30-year-old G1 P1 mother. The pregnancy was complicated by preterm labor starting at 20 weeks, and a cervical cerclage was performed. A month later the mother was again hospitalized with prolonged rupture of membrane (PROM) and preterm labor. This time the efforts to stop labor were unsuccessful, and the infant was delivered vaginally 48 hours after a single course of betamethasone was administered.

The infant's Apgar scores were 4 and 7. The infant was intubated in the delivery room due to poor respiratory effort, and an initial dose of surfactant was administered. The infant was placed immediately into a polyurethane bag for reduction of evaporative heat and fluid loss in the delivery room. Upon arrival in the NICU, the infant was placed on a combination radiant warmer/incubator table for insertion of umbilical catheters. The skin was prepared with a disinfectant (2% chlorhexidine in 70% isopropyl alcohol) prior to placing umbilical catheters. After catheters were placed and position was confirmed with a radiograph, the disinfectant was wiped away using normal saline. At this time, the top of the heating device was lowered and converted to a convectively heated incubator with RH set at 80%.

The infant's skin was very moist and fragile in appearance. After placement of the umbilical catheters, although the periumbilical skin was cleansed with sterile water to remove the skin disinfectant, the skin was noted to be more erythematous than prior to insertion. A temperature probe was attached to the abdomen with a hydrogel electrode, which promptly slid off as a result of the high humidity in the environment. An adhesive-backed foil probe cover was used to secure the catheter.

■ **Differential Diagnosis.** The chief differential diagnoses for an extremely premature infant with skin breakdown include trauma from adhesive removal, chemical burn from disinfectant used for periumbilical skin preparation, and infection. Although the original problem may be trauma, the wound can also be infected by microorganisms on the skin surface.

■ **Diagnostic Tests.** A skin culture with Gram stain and KOH prep is obtained from the area of breakdown. A CBC is obtained, as well as a blood culture. Although a catheter urine culture is requested, this is not obtained due to the extremely small size of the infant's penis and urethra; a "clean" bag specimen is collected instead.

■ **Working Diagnosis.** The Gram stain and KOH prep show budding yeast within 24 hours. The skin culture later shows a heavy growth of *C. albicans*. The blood and urine show no growth of microorganisms after 72 hours. The white blood cell remains unchanged from the first sample sent on the day of admission, but the platelet count has dropped from 100,000 to 60,000.

■ **Development of Management Plan.** After the Gram stain and KOH prep report, the area of breakdown appeared more extensive and the skin over the abdomen erythematous. The excoriated skin was gently debrided using a 30 mL syringe with warmed, one-half normal saline gently squirted through a 20-gauge Teflon catheter. Antifungal ointment, rather than cream or powder, was selected for topical treatment because of the potential healing benefits of ointments.

Because of the proximity of the excoriation to the umbilical catheter insertions, a decision was made to place a percutaneously inserted central line and peripheral arterial line so that the umbilical catheters could be discontinued.

■ **Implementation and Evaluation of Effectiveness.** After receiving the preliminary culture report and noting the drop in platelet count, it was determined that further evaluation for systemic illness would be necessary. A subsequent platelet count was 45,000, and this, coupled with the need for dopamine infusion for hypotension, prompted the medical decision to initiate systemic antifungal treatment. Fluconazole infusion was begun and a platelet transfusion was also administered.

After a second platelet transfusion, the platelet count had stabilized at 90,000 by the fifth day of treatment with fluconazole.

Despite having no growth of *C. albicans* from blood or urine samples, fungal infections in extremely premature infants can initially be cutaneous infections. If not treated early, this can quickly progress to disseminated *Candida* infections involving the blood, urinary tract, cerebrospinal fluid, or other organs.

Factors associated with cutaneous fungal infections in the first week of life are instrumentation procedures, such as cerclage placement, and PROMs. The infant can be colonized from maternal fungal or bacterial flora. Additional risk factors are skin breakdown from trauma or irritation and glucosuria. Several authors recommend early, aggressive management of cutaneous manifestations of fungal infection to prevent further dissemination and systemic complications.

ONLINE RESOURCES

Association of Women's Health, Obstetric, and Neonatal Nurses. (2014). *New neonatal skin care evidence-based practice guideline*. Retrieved from https://nwhjournal.org/article/s1751-4851(15)30804-7/abstract

Lund, C. (2018). *Presentation information. Highlights from the neonatal skin care guideline*. Retrieved from https://www.goldneonatal.com/conference/presentations/362

REFERENCES

Ackerman, A. (1985). Structure and function of the skin. In S. Moschella & H. Hurley (Eds.), *Dermatology* (2nd ed., Vol. 2). Philadelphia, PA: Saunders.

Adam, R. (2008). Skin care of the diaper area. *Pediatric Dermatology, 25*(4), 427–433. doi:10.1111/j.1525-1470.2008.00725.x

Agren, J., Sjors, G., & Sedin, G. (1998). Transepidermal water loss in infants born at 24 and 25 weeks of gestation. *Acta Paediatrica, 87*(11), 1185–1190. doi:10.1111/j.1651-2227.1998.tb00928.x

Agren, J., Sjors, G., & Sedin, G. (2006). Ambient humidity influences the rate of skin barrier maturation in extremely preterm infants. *The Journal of Pediatrics, 148*, 613–617. doi:10.1016/j.jpeds.2005.11.027

Aitken, J., & Williams, F. L. R. (2014). A systematic review of thyroid dysfunction in preterm neonates exposed to topical iodine. *Archives of Disease in Childhood—Fetal and Neonatal Edition, 99*(1), F21–F28. doi:10.1136/archdischild-2013-303799

Alvarez-Suarez, J., Gasparrini, M., Forbes-Hernández, T., Mazzoni, L., & Giampieri, F. (2014). The composition and biological activity of honey: A focus on Manuka honey. *Foods, 3*, 420–432. doi:10.3390/foods3030420

Amaya, R. (2015). Safety and efficacy of active *Leptospermum* honey in neonatal and paediatric wound debridement. *Journal of Wound Care, 24*, 95–103. doi:10.12968/jowc.2015.24.3.95

Amjad, I., Murphy, T., Nylander-Housholder, L., & Ranft, A. (2011). A new approach to management of intravenous infiltration in pediatric patients: Pathophysiology, classification, and treatment. *Journal of Infusion Nursing, 34*, 242–249. doi:10.1097/NAN.0b013e31821da1b3

Andersen, C., Hart, J., Vemgal, P., & Harrison, C. (2005). Prospective evaluation of a multi-factorial prevention strategy on the impact of nosocomial infection in very-low-birthweight infants. *Journal Hospital Infection, 61*(2), 162–167. doi:10.1016/j.jhin.2005.02.002

Anderson, G. C., Lane, A. E., & Chang, H.-P. (1995). Axillary temperature in transitional newborn infants before and after tub bath. *Applied Nursing Research, 8*(3), 123–128. doi:10.1016/S0897-1897(95)80591-5

Anderson, J., Clockburn, F., Forfar, J., Harkness, R. A., Kelly, R. W., & Kilshaw, B. (1981). Neonatal spongioform myelinopathy after restricted application of hexacholorophene skin disinfectant. *Journal of Clinical Pathology, 34*, 25–29. doi:10.1136/jcp.34.1.25

Association of Women's Health, Obstetric, and Neonatal Nurses. (2018). *Neonatal skin care*: *Evidence-based clinical practice guideline* (4th ed.). Washington, DC: Author. Retrieved from https://www.awhonn.org/store/ViewProduct.aspx?id=11678739

August, D. L., Ireland, S., & Benton, J. (2015). Silver-based dressing in an extremely low-birth-weight infant: A case study. *Journal of Wound, Ostomy, and Continence Nursing, 42*, 290–293. doi:10.1097/WON.0000000000000138

Baley, J. E., & Silverman, R. A. (1988). Systemic candidiasis: Cutaneous manifestations in low birth weight infants. *Pediatrics, 82*(2), 211–215. Retrieved from https://pediatrics.aappublications.org/content/82/2/211

Banta, C., & Noerr, B. (1992). Hyaluronidase. *Neonatal Network, 11*(6), 103–105.

Behrendt, H., & Green, M. (1971). *Patterns of skin pH from birth through adolescence*. Springfield, IL: Charles C. Thomas.

Benjamin, D. K., Stoll, B., Gantz, M., Walsh, M., Sanchez, P., Das, A., & Goldberg, R. (2010). Neonatal candidiasis: Epidemiology, risk factors, and clinical judgement. *Pediatrics, 126*, e865–e873. doi:10.1542/peds.2009-3412

Beresford, D. (2015). MHRA report chlorhexidine solutions: Risk of chemical burn injury to skin in premature infants. *Journal of Neonatal Nursing, 21*, 47–49. doi:10.1016/j.jnn.2015.02.002

Bhatia, J. (2006). Fluid and electrolyte management in the very low birth weight neonate. *Journal of Perinatology, 26*(Suppl. 1), S19–S21. doi:10.1038/sj.jp.7211466

Bissinger, R. L., & Annibale, D. J. (2010). Thermoregulation in very low-birth-weight infants during the golden hour: Results and implications. *Advances in Neonatal Care, 10*, 230–238. doi:10.1097/ANC.0b013e3181f0ae63

Black, P. (2007). Peristomal skin care: An overview of available products. *British Journal of Nursing, 16*, 1048–1056. doi:10.12968/bjon.2007.16.17.27249

Blume-Peytavi, U., & Wahn, U. (2011). Optimizing the treatment of atopic dermatitis in children: A review of the benefit/ risk ratio of methylprednisone aceponate. *Journal of the European Academy of Dermatology and Venereology, 25*, 508–515. doi:10.1111/j.1468-3083.2010.03942.x

Boswell, N., & Waker, C. L. (2016). Comparing 2 adhesive methods on skin integrity in the high-risk neonate. *Advances in Neonatal Care, 16*, 449–454. doi:10.1097/ANC.0000000000000333

Boyar, V., Handa, D., Clemens, K., & Shimborske, D. (2014). Clinical experience with *Leptospermum* honey use for treatment of hard to heal neonatal wounds: Case series. *Journal of Perinatology, 34*, 161–163. doi:10.1038/jp.2013.158

Brandon, D. H., Coe, K., Hudson-Barr, D., Oliver, T., & Landerman, L. R. (2010). Effectiveness of no-sting skin protectant and aquaphor on water loss and skin integrity in premature infants. *Journal of Perinatology, 30*(6), 414–419. doi:10.1038/jp.2009.174

Brennan, M. R., Milne, C. T., Agrell-Kahn, M., & Ekholm, B. P. (2017). Clinical evaluation of a skin protectant for management of incontinence-associated dermatitits: An open label, nonrandomized, prospective study. *Journal of Wound Ostomy Incontinence Nursing, 44*(2), 172–180. doi:10.1097/WON.0000000000000307

Bringué Espuny, X., Soria, X., Solé, E., Garcia, J., Marco, J. J., Ortega, J., . . . Pueyo, A. (2010). Chlorhexidine-methanol burns in two extreme preterm newborns. *Pediatric Dermatology, 27*, 676–678. doi:10.1111/j.1525-1470.2010.01178.x

Bromiker, R., Bin-Nun, A., Schimmel, M. S., Hammerman, C., & Kaplan, M. (2012). Neonatal hyperbilirubinemia in the low-intermediate–risk category on the bilirubin nomogram. *Pediatrics, 130*(3), e470–e475. doi:10.1542/peds.2012-0005

Bryanton, J., Walsh, D., Barrett, M., & Gaudet, D. (2004). Tub bathing versus traditional sponge bathing for the newborn. *Journal of Obstetric Gynecologic and Neonatal Nursing, 33*(6), 704–712. doi:10.1177/0884217504270651

Çaka, S. Y., & Gözen, D. (2017). Effects of swaddled and traditional tub bathing methods on crying and physiological responses of newborns. *Journal for Specialists in Pediatric Nursing, 23*, e12202. doi:10.1111/jspn.12202

Casanova, D., Bardot, J., & Magalon, G. (2001). Emergency treatment of accidental infusion leakage in the newborn: Report of 14 cases. *British Journal of Plastic Surgery, 54*(5), 396–399. doi:10.1054/bjps.2001.3593

Centers for Disease Control and Prevention. (1973). Neuropathology in newborn infants bathed with hexachlorophene. *Morbidity and Mortality Weekly Report, 22*, 93–94.

Chaiyakunapruk, N., Veenstra, D. L., Lipsky, B. A., & Saint, S. (2002). Chlorhexidine compared with povidone-iodine solution for vascular catheter-site care: A meta-analysis. *Annals of Internal Medicine, 136*(11), 792–801. doi:10.7326/0003-4819-136-11-200206040-00007

Chan, Y.-C., & Tay, Y.-K. (2015). Hypopigmentation disorders. In L. F. Eichenfield & I. J. Frieden (Eds.), *Neonatal and infant dermatology* (3rd ed., pp. 369–387). Philadelphia, PA: Elsevier Saunders.

Chandavasu, O., Garrow, E., Valda, V., Alsheikh, S., & Dela Vega, S. (1986). A new method for the prevention of skin sloughs and necrosis secondary to intravenous infiltration. *American Journal of Perinatology, 3*(1), 4–5. doi:10.1055/s-2007-999813

Chapman, A. K., Aucott, S. W., Gilmore, M. M., Advani, S., Clarke, W., & Milstone, A. M. (2013). Absorption and tolerability of aqueous chlorhexidine gluconate used for skin antisepsis prior to catheter insertion in preterm neonates. *Journal of Perinatology, 33*, 768–771. doi:10.1038/jp.2013.61

Chen, T., Eichenfield, L., & Friedlander, S. (2013). Infantile hemangiomas: An update on pathogenesis and therapy. *Pediatrics, 131*(1), 99–108. doi:10.1542/peds.2012-1128

Cheng, C. E., & Kroshinsky, D. (2011). Iatrogenic skin injury in hospitalized patients. *Clinics in Dermatology, 29*, 622–632. doi:10.1016/j.clindermatol.2011.08.006

Clark, D., & Thompson, J. (1986). Dermatology of the newborn, Parts 1 and 2. In *Pathology of the neonate slide series*, (Vol. 3, No. 4). Philadelphia, PA: Wyeth-Ayerst Laboratories.

Cole, J., Brissette, N., & Lunardi, B. (1999). Tub baths or sponge baths for newborn infants? *Mother Baby Journal, 4*, 39–43.

Colwell, A. (2015). To bathe or not to bathe: The neonatal question. *Neonatal Network, 34*, 216–219. doi:10.1891/0730-0832.34.4.216

Conner, J. M., Soll, R. F., & Edwards, W. H. (2004). Topical ointment for preventing infection in preterm infants. *Cochrane Database of Systematic Review,* (1), CD001150. doi:10.1002/14651858.cd001150

Cooper, P. (2010). Appeel Sterile sachet: Helps remove pain from a dressing change. *Wounds UK, 6*, 100–106.

Cooper, P., Russell, F., Stringfellow, S., Duguid, K., & Pirie, G. (2011). The use of Appeel® Sterile sachet to treat a very old and a very young patient. *Wounds UK, 7*, 124–127.

Coughlin, C., Frieden, I., & Eichenfield, L. (2014). Clincal approaches to skin cleansing of the diaper area: Practice and challenges. *Pediatric Dermatology, 31*(Suppl. 1), 1–4. doi:10.1111/pde.12461

Cousins, Y. (2014). Wound care considerations in neonates. *Nursing Standard, 28*(46), 61–70. doi:10.7748/ns.28.46.61.e8402

Cunningham, B. B., & Wagner, A. M. (2008). Diagnostic and therapeutic procedures. In L. A. Eichenfield, I. J. Frieden, & N. B. Esterly (Eds.), *Neonatal dermatology* (2nd ed., pp. 73–84). Philadelphia, PA: Saunders Elsevier.

Curley, M. A. Q., Hasbani, N. R., Quigley, S. M., Stellar, J. J., Pasek, T. A., Shelley, S. S., . . . Wypij, D. (2018). Predicting pressure injury risk in pediatric patients: The Braden QD Scale. *Journal of Pediatrics, 192*, 189–195.e2. doi:10.1016/j.jpeds.2017.09.045

Curley, M. A. Q., Razmus, I. S., Roberts, K. E., & Wypij, D. (2003). Predicting pressure ulcer risk in pediatric patients: The Braden Q scale. *Nursing Research, 52*(1), 22–33. doi:10.1097/00006199-200301000-00004

da Cunha, M., & Procianoy, R. (2005). Effect of bathing on skin flora of preterm newborns. *Journal of Perinatology, 25*, 375–379. doi:10.1038/sj.jp.7211332

Darmstadt, G. L., & Dinulos, J. G. (2000). Neonatal skin care. *Pediatric Clinics of North America, 47*, 757–782. doi:10.1016/S0031-3955(05)70239-X

Darmstadt, G. L., Dinulos, J., & Miller, Z. (2000). Congenital cutaneous candidiasis: Clinical presentation, pathogenesis, and management guidelines. *Pediatrics, 105*, 438–444. doi:10.1542/peds.105.2.438

Davies, J., Gault, D., & Buchdahl, R. (1994). Preventing the scars of neonatal intensive care. *Archives of Disease in Childhood—Fetal and Neonatal Editions, 70*(1), F50–F51. doi:10.1136/fn.70.1.F50

Deckers, I. A., McLean, S., Linssen, S., Mommers, M., van Schayck, C., & Sheikh, A. (2012). Investigating international time trends in the incidence and prevalence of atopic eczema 1190–2010: A systematic review of epidemiological studies. *PLoS One, 7*, e39803. doi:10.1371/journal.pone.0039803

Denyer, J. (2011). Reducing pain during the removal of adhesive and adherent products. *British Journal of Nursing, 20*(Suppl. 8), S28–S35. doi:10.12968/bjon.2011.20.Sup8.S28

de Waard-van der Spek, F., Andresen, K., Darsow, U., Mortz, C., Orton, D., Worm, M., & Oranje, P. (2013). Allergic contact dermatitis in children: Which factors are relevant? (Review of the literature). *Pediatric Allergy and Immunology, 24*, 321–329. doi:10.1111/pai.12043

Dinulos, J. G., & Darmstadt, G. L. (2005). Dermatologic conditions. In M. G. MacDonald, M. D. Mullett, & M. K. Seshia (Eds.), *Avery's neonatology: Pathophysiology and management of the newborn* (6th ed., pp. 1485–1505). Philadelphia, PA: Lippincott Williams & Wilkins.

Dinulos, J. G., & Pace, N. C. (2008). Bacterial infections. In L. A. Eichenfield, I. J. Frieden, & N. B. Esterly (Eds.), *Neonatal dermatology* (2nd ed., pp. 173–192). Philadelphia, PA: Saunders Elsevier.

Dizon, M., Galzote, C., Estanislao, R., Matthew, N., & Sarkar, R. (2010). Tolerance of baby cleansers in infants: A randomized controlled trial. *Indian Pediatrics, 47*, 959–963. doi:10.1007/s13312-010-0161-8

Dominguez-Bello, M. G., Costello, E. K., Contreras, M., Magris, M., Hidalgo, G., Fierer, N., & Knight, R. (2010). Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proceedings of the National Academy of Sciences of the United States of America, 107*(26), 11971–11975. doi:10.1073/pnas.1002601107

Droitcourt, C., Kerbrat, S., Rault, C., Botrel, M., Happe, A., Garlantezed, R., . . . Dupuy, A. (2018). Safety of oral propranolol for infantile hemangioma. *Pediatrics, 141*(6), e2173783 doi:10.1542/peds.2017-3783

Drolet, B., Frommelt, P., Chamlin, S., Haggstrom, A., Bauman, M., Chiu, Y., . . . & Frieden, I. (2013). Initiation and use of propranolol for infantile hemangioma: Report of a consensus conference. *Pediatrics, 131*(1), 128–139. doi:10.1542/peds.2012-1691

Dyer, J. A. (2013). Newborn skin care. *Seminars in Perinatology, 37*, 3–7. doi:10.1053/j.semperi.2012.11.008

Edraki, M., Paran, M., Montaseri, S., Razavi Nejad, M., & Montaseri, Z. (2014). Comparing the effects of swaddled and conventional bathing methods on body temperature and crying duration in premature infants: A randomized clinical trial. *Journal of Caring Sciences, 3*, 83–91. doi:10.5681/jcs.2014.009

Edwards, W. H., Conner, J. M., & Soll, R. F. (2004). The effect of prophylactic ointment therapy on nosocomial sepsis rates and skin integrity in infants with birth weights of 501 to 1000 g. *Pediatrics, 113*(5), 1195–1203. doi:10.1542/peds.113.5.1195

Ehretsmann, C., Schaefer, P., & Adam, R. (2001). Cutaneous tolerance of baby wipes by infants with atopic dermatitis, and comparison of the mildness of baby wipe and water in infant skin. *Journal of the European Academy of Dermatology Venereology, 15*(Suppl. 1), 16–21. doi:10.1046/j.0926-9959.2001.00004.x

Enjolras, O., & Garzon, M. C. (2008). Vascular stains, malformations and tumors. In L. A. Eichenfield, I. J. Frieden, & N. B. Esterly (Eds.), *Neonatal dermatology* (2nd ed., pp. 343–374). Philadelphia, PA: Saunders Elsevier.

Esser, M. (2016). Diaper dermatitis: What do we do next? *Advances in Neonatal Care, 16*(Suppl. 5S), S21–S25. doi:10.1097/ANC.0000000000000316

Esser, M. (2017). *Leptospermum* honey for wound care in an extremely premature infant. *Advances in Neonatal Care, 17*, 27–32. doi:10.1097/ANC.0000000000000331

Fern, D., Graves, C., & L'Huillier, M. (2002). Swaddled bathing in the newborn intensive care unit. *Newborn and Infant Nursing Reviews, 2*, 3–4. doi:10.1053/nbin.2002.31481

Fernandes, J. D., Machado, M. C., & Oliveira, A. N. (2011). Children and newborn skin care and prevention. *Anais Brasileiros de Dermatologica, 86*, 102–110. doi:10.1590/S0365-05962011000100014

Fields, K. S., Nelson, T., & Powell, D. (2006). Contact dermatitis caused by baby wipes. *Journal of the American Academy Dermatology, 54*(5 Suppl.), S230–S232. doi:10.1016/j.jaad.2005.10.024

Fox, C., Nelson, D., & Wareham, J. (1998). The timing of skin acidification in very low birth weight infants. *Journal of Perinatology, 18*(4), 272–275.

Fox, M. D. (2011). Wound care in the neonatal intensive care unit. *Neonatal Network, 30*(5), 291–303. doi:10.1891/0730-0832.30.5.291

Friedlander, S. F., & Bradley, J. S. (2008). Viral infections. In L. A. Eichenfield, I. J. Frieden, & N. B. Esterly (Eds.), *Neonatal dermatology* (2nd ed., pp. 192–212). Philadelphia, PA: Saunders Elsevier.

Garcia Bartels, N., Scheufele, R., Prosch, F., Schink, T., Proquitté, H., Wauer, R. R., & Blume-Peytavi, U. (2010). Effect of standardized skin care regimens on neonatal skin barrier function in different body areas. *Pediatric Dermatology, 27*, 1–8. doi:10.1111/j.1525-1470.2009.01068.x

Garland, J. S., Alex, C. P., Uhing, M. R., Peterside, I. E., Rentz, A., & Harris, M. C. (2009). Pilot trial to compare tolerance of chlorhexidine gluconate to povidone-iodine antisepsis for central venous catheter placement in neonates. *Journal of Perinatology, 29*(12), 808–813. doi:10.1038/jp.2009.161

Garland, J. S., Buck, R. K., Maloney, P., Durkin, D. M., Toth-Lloyd, S., Duffy, M., . . . Goldmann, D. (1995). Comparison of 10% povidone-iodine and 0.5% chlorhexidine gluconate for the prevention of peripheral intravenous catheter colonization in neonates: A prospective trial. *Pediatric Infectious Disease Journal, 14*(6), 510–516. doi:10.1097/00006454-199506000-00008

Gfatter, R., Hackl, P., & Braun, F. (1997). Effects of soap and detergents on skin surface pH, stratum corneum hydration and fat content in infants. *Dermatology, 195*(3), 258–262. doi:10.1159/000245955

Gilliam, A. E., & Williams, M. L. (2008). Skin of the premature infant. In L. A. Eichenfield, I. J. Frieden, & N. B. Esterly (Eds.), *Neonatal dermatology* (2nd ed., pp. 45–58). Philadelphia, PA: Saunders Elsevier.

Gopalakrishnan, P. N., Goel, N., & Banerjee, S. (2017). Saline irrigation for the management of skin extravasation injury in neonates. *Cochrane Database of Systematic Reviews*, (2), CD008404. doi:10.1002/14651858.CD008404.pub2

Gorski, L. A., Stranz, M., Cook, L. S., Joseph, J. M., Kokotis, K., Sabatino-Holmes, P., . . . Infusion Nurses Society Vesicant Task Force. (2017). Development of an evidence-based list of noncytotoxic vesicant medications and solutions. *Journal of Infusion Nursing, 40*, 26–40. doi:10.1097/NAN.0000000000000202

Gras-Le Guen, C., Caille, A., Launay, E., Boscher, C., Godon, N., Savagner, C., . . . Giraudeau, B. (2017). Dry care versus antiseptics for umbilical cord care: A cluster randomized trial. *Pediatrics, 139*, e20161857. doi:10.1542/peds.2016-1857

Gregory, K. E. (2011). Microbiome aspects of perinatal and neonatal health. *Journal of Perinatal Neonatal Nursing, 25*(2), 158–162. doi:10.1097/JPN.0b013e3182169346

Grove, G. L., Zerweck, C. R., Ekholm, B. P., Smith, G. E., & Koski, N. I. (2014). Randomized comparison of a silicone tape and a paper tape for gentleness in healthy children. *Journal of Wound, Ostomy, and Continence Nursing, 41*, 40–48. doi:10.1097/01.WON.0000436669.79024.b0

Haggstrom, A. N., & Chamlin, S. L. (2014). Infantile hemangiomas and other vascular tumors. In L. Eichenfield & I. Frieden (Eds), *Neonatal and infant dermatology* (3rd ed., pp. 336–351). Philadelphia, PA: Elsevier Saunders.

Hammarlund, K., & Sedin, G. (1979). Transepidermal water loss in newborn infants. III. Relation to gestational age. *Acta Paediatrica Scandinavica, 68*(6), 795–801. doi:10.1111/j.1651-2227.1979.tb08214.x

Harpin, V. A., & Rutter, N. (1983). Barrier properties of the newborn infant's skin. *Journal of Pediatrics, 102*(3), 419–425. doi:10.1016/S0022-3476(83)80669-6

Haubrich, K. A. (2003). Role of vernix caseosa in the neonate: Potential application in the adult population. *AACN Clinical Issues, 14*(4), 457–464. doi:10.1097/00044067-200311000-00006

Heimall, L. M., Storey, B., Stellar, J. J., & Davis, K. F. (2012). Beginning at the bottom: Evidence-based care of diaper dermatitis. *MCN The American Journal of Maternal Child Nursing, 37*(1), 10–16. doi:10.1097/NMC.0b013e31823850ea

Hennigsson, A., Nystrom, B., & Tunnel, R. (1981). Bathing or washing babies after birth. *Lancet, 19*, 1401–1403. doi:10.1016/S0140-6736(81)92812-9

Herane, M. I., & Ando, I. (2003). Acne in infancy and acne genetics. *Dermatology, 206*(1), 24–28. doi:10.1159/000067819

Hoath, S. B., & Narendran, V. (2000). Adhesives and emollients in the preterm infant. *Seminars in Neonatology, 5*(4), 289–296. doi:10.1053/siny.2000.0015

Hoath, S. B., & Narendran. V. (2015). The skin of the neonate. In R. J. Martin, A. Fanaroff, & M. Walsh (Eds.), *Fanaroff & Martin's neonatal-perinatal medicine: Diseases of the fetus and infant* (10th ed.). Philadelphia, PA: Saunders Elsevier.

Hoeger, P. H., & Enzmann, C. C. (2002). Skin physiology of the neonate and young infant: A prospective study of functional skin parameters during early infancy. *Pediatric Dermatology, 19*(3), 256–262. doi:10.1046/j.1525-1470.2002.00082.x

Holbrook, K. A. (1982). A histological comparison of infant and adult skin. In H. I. Maibach & E. K. Boisits (Eds.), *Neonatal skin: Structure and function*. New York, NY: Marcel Dekker.

Hook, K. P., & Eichenfield, L. F. (2011). Approach to the neonate with ecchymoses and crusts. *Dermatologic Therapy, 24*(2), 240–248. doi:10.1111/j.1529-8019.2011.01399.x

Horimukai, K., Morita, K., Narita, M., Kondo, M., Kitazawa, H., Nozaki, M., . . . Ohya, Y. (2014). Application of moisturizer to neonates prevents development of atopic dermatitis. *Journal of Allergy and Clinical Immunology, 134*, 824–830.e6. doi:10.1016/j.jaci.2014.07.060

Howard, R., & Frieden, I. J. (2015). Vesicles, pustules, bullae, erosions, and ulcerations. In L. A. Eichenfield & I. J. Frieden (Eds.), *Neonatal and infant dermatology* (3rd ed., p. 111–139). Philadelphia, PA: Elsevier Saunders.

Hsu, W.-C., Yeh, L.-C., Chuang, M.-Y., Lo, W.-T., Cheng, S.-N., & Huang, C.-F. (2010). Umbilical separation time delayed by alcohol application. *Annals of Tropical Paediatrics, 30*, 219–223. doi:10.1179/146532810X12786388978643

Imdad, A., Bautista, R. M. M., Senen, K. A. A., Uy, M. E. V., Mantaring, J. B., III., & Bhutta, Z. A. (2013). Umbilical cord antiseptics for preventing sepsis and death among newborns. *Cochrane Database of Systematic Reviews*, (5), CD008635. doi:10.1002/14651858.CD008635.pub2

Irvin, E. J., & Miller, H. D. (2015). Emollient use in the term newborn: A literature review. *Neonatal Network, 34*(4), 227–230. doi:10.1891/0730-0832.34.4.227

Irving, V. (2001). Reducing the risk of epidermal stripping in the neonatal population: An evaluation of an alcohol free barrier film. *Journal of Neonatal Nursing, 7*, 5–8.

Ittmann, P. I., & Bozynski, M. E. (1993). Toxic epidermal necrolysis in a newborn infant after exposure to adhesive remover. *Journal of Perinatology, 13*(6), 476–477.

Ivich, J. (2015). Ichthyosis in the neonatal setting. *Advances in Neonatal Care, 15*(4), 253–260. doi:10.1097/ANC.0000000000000106

Jensen, C., & Glabraith, S. (2015). Iatrogenic and traumatic injuries. In L. Eichenfield & I. Frieden (Eds.), *Neonatal and infant dermatology* (3rd ed., pp. 77–93). Philadelphia, PA: Elsevier Saunders.

Kalia, Y. N., Nonato, L. B., Lund, C. H., & Guy, R. H. (1998). Development of skin barrier function in premature infants. *Journal of Investigative Dermatology, 111*(2), 320–326. doi:10.1046/j.1523-1747.1998.00289.x

Kieran, E. A., O'Sullivan, A., Miletin, J., Twomey, A. R., Knowles, S. J., & O'Donnell, C. P. F. (2018). 2% chlorhexidine–70% isopropyl alcohol versus 10% povidone–iodine for insertion site cleaning before central line insertion in preterm infants: A randomised trial. *Archives of Disease in Childhood—Fetal and Neonatal Edition, 103*(2), F101–F106. doi:10.1136/archdischild-2016-312193

Kilpatrick, S. J., Papile, L.-A., Macones, G. A. (Eds.). (2017). *Guidelines for perinatal care* (8th ed.). Elk Grove Village, IL: American Academy of Pediatrics; Washington, DC: The American College of Obstetricians and Gynecologists.

Kim, S. M., Lee, E. Y., Chen, J., & Ringer, S. A. (2010). Improved care and growth outcomes by using hybrid humidified incubators in very preterm infants. *Pediatrics, 125*(1), e137–e145. doi:10.1542/peds.2008-2997

King, A., Stellar, J., Blevins, A., & Shah, K. (2014). Dressings and products in pediatric wound care. *Advances in Wound Care, 3*, 324–334. doi:10.1089/wound.2013.0477

Kjällström, B., Sedin, G., & Ågren, J. (2011). Clothing reduces evaporative water and heat loss in preterm infants. *Journal of Neonatal-Perinatal Medicine, 4*, 89–92. doi:10.3233/NPM-2011-2745

Knobel, R. B., Wimmer, J. E., Jr., & Holbert, D. (2005). Heat loss prevention for preterm infants in the delivery room. *Journal of Perinatology, 25*(5), 304–308. doi:10.1038/sj.jp.7211289

Kostogloudis, N., Demiri, E., Tsimponis, A., Dionyssiou, D., Ioannidis, S., Chatziioannidis, I., & Nikolaidis, N. (2015). Severe extravasation injuries in neonates: A report of 34 cases. *Pediatric Dermatology, 32*, 830–835. doi:10.1111/pde.12664

Kutsch, J., & Ottinger, D. (2014). Neonatal skin and chlorhexidine: A burning experience. *Journal of Neonatal Nursing, 33*(1), 19–23. doi:10.1891/0730-0832.33.1.19

Laken, P. (2016). Infantile hemangioma: Pathogenesis and review of propranolol use. *Advances in Neonatal Care, 16*(2), 135–142. doi:10.1097/ANC.0000000000000254

Lane, A. T., & Drost, S. S. (1993). Effects of repeated application of emollient cream to premature neonates' skin. *Pediatrics, 92*(3), 415–419. Retrieved from https://pediatrics.aappublications.org/content/92/3/415

Larson, A. A., & Dinulos, J. G. (2005). Cutaneous bacterial infections in the newborn. *Current Opinion Pediatrics, 17*(4), 481–485. doi:10.1097/01.mop.0000171321.68806.bd

Lashkari, H. P., Chow, P., & Godambe, S. (2012). Aqueous 2% chlorhexidine-induced chemical burns in an extremely premature infant. *Archives of Disease in Childhood—Fetal and Neonatal Edition, 97*, F64. doi:10.1136/adc.2011.215145

Laurie, S. W., Wilson, K. L., Kernahan, D. A., Bauer, B. S., & Vistnes, L. M. (1984). Intravenous extravasation injuries: The effectiveness of hyaluronidase in their treatment. *Annals of Plastic Surgery, 13*(3), 191–194. doi:10.1097/00000637-198409000-00003

Lavender, T., Bedwell, C., Roberts, S. A., Hart, A., Turner, M. A., Carter, L. A., & Cork, M. J. (2013). Randomized, controlled trial evaluating a baby wash product on skin barrier function in healthy, term neonates. *Journal of Obstetric, Gynecologic, and Neonatal Nursing, 42*, 203–214. doi:10.1111/1552-6909.12015

Lavender, T., Furber, C., Campbell, M., Victor, S., Roberts, I., Bedwell, C., & Cork, M. J. (2012). Effect on skin hydration of using baby wipes to clean the napkin area of newborn babies: Assessor-blinded randomised controlled equivalence trial. *BMC Pediatrics, 12*, 59. doi:10.1186/1471-2431-12-59

Lawton, S. (2013). Understanding skin care and skin barrier function in infants. *Nursing Children and Young People, 25*(7), 28–33. doi:10.7748/ncyp2013.09.25.7.28.e358

Liaw, J.-J., Yang, L., Chou, H.-L., Yang, M.-H., & Chao, S.-C. (2010). Relationships between nurse care-giving behaviours and preterm

infant responses during bathing: A preliminary study. *Journal of Clinical Nursing, 19*(1/2), 89–99. Retrieved from https://onlinelibrary.wiley.com/doi/full/10.1111/j.1365-2702.2009.03038.x

Liaw, J.-J., Yang, L., Yuh, Y.-S., & Yin, T. (2006). Effects of tub bathing procedures on preterm infants' behavior. *The Journal of Nursing Research, 14*, 297–305. doi:10.1097/01.JNR.0000387589.12340.98

Lin, H.-C., Lin, H.-Y., Su, B.-H., Ho, M.-W., Ho, C.-M., Lee, C.-Y., . . . Lu, J.-J. (2013). Reporting an outbreak of *Candida pelliculosa* fungemia in a neonatal intensive care unit. *Journal of Microbiology, Immunology and Infection, 46*, 456–462. doi:10.1016/j.jmii.2012.07.013

Linder, N., Davidovitch, N., Reichman, B., Kuint, J., Lubin, D., Meyerovitch, J., . . . Sack, J. (1997). Topical iodine-containing antiseptics and subclinical hypothyroidism in preterm infants. *Journal of Pediatrics, 131*(3), 434–439. doi:10.1016/S0022-3476(97)80071-6

Lineaweaver, W., Howard, R., Soucy, D., McMorris, S., Freeman, J., Crain, C., . . . Rumley, T. (1985). Topical antimicrobial toxicity. *Archives of Surgery, 120*, 267–270. doi:10.1001/archsurg.1985.01390270007001

Lo, J. S., Oriba, H. A., Maibach, H. I., & Bailin, P. L. (1990). Transepidermal potassium ion, chloride ion, and water flux across delipidized and cellophane tape-stripped skin. *Dermatologica, 180*(2), 66–68. doi:10.1159/000247992

Loomis, C. A., Koss, T., & Chu, D., (2008). Fetal skin development. In L. A. Eichenfield, I. J. Frieden, & N. B. Esterly (Eds.), *Neonatal dermatology* (2nd ed., pp. 1–18). Philadelphia, PA: Saunders Elsevier.

Loring, C., Gregory, K., Gargan, B., LeBlanc, V., Lundgren, D., Reily, J., . . . Zaya, C. (2012). Tub bathing improves thermoregulation of the late preterm infant. *Journal of Obstetric, Gynecologic, and Neonatal Nursing, 41*, 171–179. doi:10.1111/j.1552-6909.2011.01332.x

Loveday, H. P., Wilson, J. A., Pratt, R. J., Golsorkhi, M., Tingle, A., Bak, A., . . . Wilcox, M. (2014). Epic3: National evidence-based guidelines for preventing healthcare associated infections in NHS hospitals in England. *Journal of Hospital Infection, 86*, S1–S70. Retrieved from https://scholar.google.com/citations?user=oij7HwgAAAAJ&hl=en&oi=sra#d=gs_md_cita-d&u=%2Fcitations%3Fview_op%3Dview_citation%26hl%3Den%26user%3Doij7HwgAAAAJ%26citation_for_view%3Doij7HwgAAAAJ%3Ad1gkVwhDpl0C%26tzom%3D240

Lucky, A. W. (2008). Transient benign cutaneous lesions in the newborn. In L. A. Eichenfield, I. J. Frieden, & N. B. Esterly (Eds.), *Neonatal dermatology* (2nd ed., pp. 85–98). Philadelphia, PA: Saunders Elsevier.

Lucky, A. W. (2015). Transient benign cutaneous lesions in the newborn. In L. Eichenfield & I. Frieden (Eds.), *Neonatal and infant dermatology* (3rd ed., pp. 65–76). Philadelphia, PA: Elsevier Saunders.

Lund, C. (2014). Medical adhesives in the NICU. *Newborn and Infant Nursing Reviews, 14*, 160–165. doi:10.1053/j.nainr.2014.10.001

Lund, C., Kuller, J., Lane, A., Lott, J. W., & Raines, D. A. (1999). Neonatal skin care: The scientific basis for practice. *Journal of Obstetrics, Gynecology, and Neonatal Nursing, 28*(3), 241–254. doi:10.1111/j.1552-6909.1999.tb01989.x

Lund, C., & Tucker, J. (2003). Skin adhesion. In S. B. Hoath & H. I. Maibach (Eds.), *Neonatal skin: Structure and function* (2nd ed.). New York, NY: Marcel Dekker.

Lund, C. H., Nonato, L. B., Kuller, J. M., Franck, L. S., Cullander, C., & Durand, D. J. (1997). Disruption of barrier function in neonatal skin associated with adhesive removal. *Journal of Pediatrics, 131*(3), 367–372. doi:10.1016/S0022-3476(97)80060-1

Lund, C. H., & Osborne, J. W. (2004). Validity and reliability of the neonatal skin condition score. *Journal of Obstetrics, Gynecology and Neonatal Nursing, 33*(3), 320–327. doi:10.1177/0884217504265174

Lund, C. H., Osborne, J. W., Kuller, J., Lane, A. T., Lott, J. W., & Raines, D. A. (2001). Neonatal skin care: Clinical outcomes of the AWHONN/NANN evidence-based clinical practice guideline. Association of Women's Health, Obstetric and Neonatal Nurses and the National Association of Neonatal Nurses. *Journal of Obstetrics, Gynecology, and Neonatal Nursing, 30*(1), 41–51. doi:10.1111/j.1552-6909.2001.tb01520.x

Mancini, A. J. (2004). Skin. *Pediatrics, 113*(Suppl. 3), 1114–1119. Retrieved from https://pediatrics.aappublications.org/content/113/Supplement_3/1114

Mannan, K., Chow, P., Lissauer, T., & Godambe, S. (2007). Mistaken identify of skin cleansing solution leading to extensive chemical burns in an extremely preterm infant. *Acta Paediatrica, 96*(10), 1536–1537.

Marks, J. G., Belsito, D. V., DeLeo, V. A., Fowler, J. F., Fransway, A. F., Maibach, H. I., . . . Taylor, J. S. (1995). North American Contact Dermatitis Group standard tray patch test results. *American Journal of Contact Dermatitis, 6*(3), 160–165. doi:10.1016/1046-199X(95)90122-1

Marschall, J., Mermel, L. A., Fakih, M., Hadaway, L., Kallen, A., O'Grady, N. P., . . . Yokoe, D. S. (2014). Strategies to prevent central line–associated bloodstream infections in acute care hospitals: 2014 update. *Infection Control and Hospital Epidemiology, 35*, 753–771. doi:10.1086/676533

Mavropoulos, J., & Cohen, B. (2013). Disorders of pigmentation. In B. Cohen (Ed.), *Pediatric dermatology* (4th ed.). Philadelphia, PA: Saunders Elsevier.

McNichol, L., Lund, C., Rosen, T., & Gray, M. (2013). Medical adhesives and patient safety: State of the science. *Journal of Wound, Ostomy and Continence Nursing, 40*, 365–380. doi:10.1097/WON.0b013e3182995516

Milstone, A. M., Bamford, P., Aucott, S. W., Tang, N., White, K. R., & Bearer, C. F. (2014). Chlorhexidine inhibits L1 cell adhesion molecule-mediated neurite outgrowth in vitro. *Pediatric Research, 75*, 8–13. doi10.1038/pr.2013.175

Milstone, A. M., Elward, A., Song, X., Zerr, D. M., Orscheln, R., Speck, K., . . . Perl, T. M. (2013). Daily chlorhexidine bathing to reduce bacteraemia in critically ill children: A multicentre, cluster-randomised, crossover trial. *Lancet, 381*, 1099–1106. doi:10.1016/S0140-6736(12)61687-0

Milstone, A. M., Passaretti, C. L., & Perl, T. M. (2008). Chlorhexidine: Expanding the armamentarium for infection control and prevention. *Clinical Infectious Diseases, 46*(2), 274–281. doi:10.1086/524736

Mohr, L. D., Reyna, R., & Amaya, R. (2014). Neonatal case studies using active *Leptospermum* honey. *Journal of Wound, Ostomy, and Continence Nursing, 41*, 213–218. doi:10.1097/WON.0000000000000028

Moore, K. L., & Persaud, T. V. N. (2015). *The developing human: Clinically oriented embryology* (10th ed.). Philadelphia, PA: Saunders Elsevier.

Moraille, R., Pickens, W. L., Visscher, M. O., & Hoath, S. B. (2005). A novel role for vernix caseosa as a skin cleanser. *Biology of the Neonate, 87*(1), 8–14. doi:10.1159/000080488

Neri, I., Ravaioli, G. M., Faldella, G., Capretti, M. G., Arcuri, S., & Patrizi, A. (2017). Chlorhexidine gluconate-induced chemical burns in very low birth weight infants. *Journal of Pediatrics, 191*, 262–265.e2. doi:10.1016/j.jpeds.2017.08.002

Newland, K., Warren, L., & Gold, M. (2013). Food allergy testing in infantile eczema: A clinical approach and algorithm. *Australasian Journal of Dermatology, 54*, 79–84. doi:10.1111/j.1440-0960.2012.00911.x

Nopper, A. J., Horii, K. A., Sookdeo-Drost, S., Wang, T. H., Mancini, A. J., & Lane, A. T. (1996). Topical ointment therapy benefits premature infants. *Journal of Pediatrics, 128*(5), 660–669. doi:10.1016/S0022-3476(96)80132-6

Nuntnarumit, P., & Sangsuksawang, N. (2013). A randomized controlled trial of 1% aqueous chlorhexidine gluconate compared with 10% povidone-iodine for topical antiseptic in neonates: Effects on blood culture contamination rates. *Infection Control and Hospital Epidemiology, 34*, 430–432. doi:10.1086/669863

O'Grady, N. P., Alexander, M., Burns, L. A., Dellinger, P., Garland, J., Heard, S. O., . . . Healthcare Infection Control Practices Adisory Committee. (2011). *Guidelines for the prevention of intravascular catheter-related infections, 2011*. Retrieved from https://www.cdc.gov/hai/pdfs/bsi-guidelines-2011.pdf

O'Neil, A., & Schumacher, B. (2014). Application of a pectin barrier for medical adhesive skin injury (epidermal stripping) in a premature infant. *Journal of Wound, Ostomy, and Continence Nursing, 41*, 219–221. doi:10.1097/WON.0000000000000029

Örge, F., & Grigorian, F. (2015). Examination and common problems of the neonatal eye. In R. Martin, A. Fanaroff, & M. Walsh (Eds.), *Fanaroff & Martin's neonatal-perinatal medicine: Diseases of the fetus and infant* (10th ed.). Philadelphia, PA: Saunders Elsevier.

Paternoster, M., Niola, M., & Graziano, V. (2017). Avoiding chlorhexidine burns in preterm infants. *Journal of Obstetric, Gynecologic and Neonatal Nursing, 46*, 267–271. doi:10.1016/j.jogn.2016.10.007

Peters, K. L. (1998). Bathing premature infants: Physiological and behavioral consequences. *American Journal of Critical Care, 7*, 90–100. Retrieved from http://ajcc.aacnjournals.org/content/7/2/90.abstract

Ponnusamy, V., Venkatesh, V., & Clarke, P. (2014). Skin antisepsis in the neonate: What should we use? *Current Opinion in Infectious Diseases, 27*, 244–250. doi:10.1097/QCO.0000000000000064

Püttgen, K., & Cohen, B. (2013). Neonatal dermatology. In B. Cohen (Ed.), *Pediatric dermatology* (4th ed.). Philadelphia, PA: Saunders Elsevier.

Quach, C., Milstone, A. M., Perpete, C., Bonenfant, M., Moore, D. L., & Perreault, T. (2014). Chlorhexidine bathing in a tertiary care neonatal intensive care unit: Impact on central line-associated bloodstream infections. *Infection Control and Hospital Epidemiology, 35*, 158–163. doi:10.1086/674862

Quinn, D., Newton, N., & Piecuch, R. (2005). Effect of less frequent bathing on premature infant skin. *Journal of Obstetrics, Gynecologic, and Neonatal Nursing, 34*, 741–746. doi:10.1177/0884217505282021

Raszka, W. V., Jr., Kueser, T. K., Smith, F. R., & Bass, J. W. (1990). The use of hyaluronidase in the treatment of intravenous extravasation injuries. *Journal of Perinatology, 10*(2), 146–149.

Reynolds, P. R., Banerjee, S., & Meek, J. H. (2005). Alcohol burns in extremely low birthweight infants: Still occurring. *Archives Disease Child Fetal and Neonatal Edition, 90*(1), F10. doi:10.1136/adc.2004.054338

Rolstad, B. S., & Ovington, L. (2007). Principles of wound management. In R. A. Byrant & D. P. Nix (Eds.), *Acute and chronic wounds: Current management concepts* (3rd ed., pp. 391–426). St. Louis, MO: Mosby.

Sardesai, S. R., Kornacka, M. K., Walas, W., & Ramanathan, R. (2011). Iatrogenic skin injury in the neonatal intensive care unit. *Journal of Maternal-Fetal & Neonatal Medicine, 24*, 197–203. doi:10.3109/14767051003728245

Sathiyamurthy, S., Banerjee, J., & Godambe, S. V. (2016). Antiseptic use in the neonatal intensive care unit—A dilemma in clinical practice: An evidence based review. *World Journal of Clinical Pediatrics, 5*, 159–171. doi:10.5409/wjcp.v5.i2.159

Sawatzky-Dickson, D., & Bodnaryk, K. (2006). Neonatal intravenous extravasation injuries: Evaluation of a wound care protocol. *Neonatal Network, 25*(1), 13–19. doi:10.1891/0730-0832.25.1.13

Schick, J. B., & Milstein, J. M. (1981). Burn hazard of isopropyl alcohol in the neonate. *Pediatrics, 68*(4), 587–588. Retrieved from https://pediatrics.aappublications.org/content/68/4/587

Sekkat, N., Kalia, Y. N., & Guy, R. H. (2004). Development of an in vitro model for premature neonatal skin: Biophysical characterization using transepidermal water loss. *Journal of Pharmacological Sciences, 93*(12), 2936–2940. doi:10.1002/jps.20195

Sethi, R., Schwartz, R. A., & Janniger, C. K. (1996). Oculocutaneous albinism. *Cutis, 57*(6), 397–401.

Shalita, A. (1981). *Principles of infant skin care*. Skillman, NJ: Johnson & Johnson Baby Products.

Siegfried, E. C. (2008). Neonatal skin care and toxicology. In L. A. Eichenfield, I. J. Frieden, & N. B. Esterly (Eds.), *Neonatal dermatology* (2nd ed., pp. 59–72). Philadelphia, PA: Saunders Elsevier.

Siegfried, E. C., & Shah, P. Y. (1999). Skin care practices in the neonatal nursery: A clinical survey. *Journal of Perinatology, 19*(1), 31–39. doi:10.1038/sj.jp.7200110

Simona, R. (2012). A pediatric peripheral intravenous infiltration assessment tool. *Journal of Infusion Nursing, 35*, 243–248. doi:10.1097/NAN.0b013e31825af323

Simpson, E. L., Berry, T., Brown, P., & Hanifin, J. (2010). A pilot study of emollient therapy for the primary prevention of atopic dermatitis. *Journal of the American Academy of Dermatology, 63*, 587–593. doi:10.1016/j.jaad.2009.11.011

Simpson, E. L., Chalmers, J. R., Hanifin, J. M., Thomas, K. S., Cork, M. J., McLean, W. H. I., . . . Williams, H. C. (2014). Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. *Journal of Allergy and Clinical Immunology, 134*, 818–823. doi:10.1016/j.jaci.2014.08.005

Smack, D. P., Harrington, A. C., Dunn, C., Howard, R. S., Szkutnik, A. J., Krivda, S. J., . . . James, W. D. (1996). Infection and allergy incidence in ambulatory surgery patients using white petrolatum vs bacitracin ointment. A randomized controlled trial. *Journal of the American Medical Association, 276*(12), 972–977. doi:10.1001/jama.1996.03540120050033

Smith, W. J., & Jacob, S. E. (2009). The role of allergic contact dermatitis in diaper dermatitis. *Pediatric Dermatology, 26*(3), 369–370. doi:10.1111/j.1525-1470.2009.00934.x

Smolinski, K. N., & Yan, A. C. (2005). Hemangiomas of infancy: Clinical and biological characteristics. *Clinical Pediatrics, 44*(9), 747–766. doi:10.1177/000992280504400902

Stamatas, G. N., Nikolovski, J., Mack, M. C., & Kollias, N. (2011). Infant skin physiology and development during the first years of life: A review of recent findings based on in vivo studies. *International Journal of Cosmetic Science, 33*(1), 17–24. doi:10.1111/j.1468-2494.2010.00611.x

Stamatas, G. N., & Tierney, N. K. (2014). Diaper dermatitis: Etiology, manifestations, prevention, and management. *Pediatric Dermatology, 31*, 1–7. doi:10.1111/pde.12245

Stewart, D., Benitz, W., & Committee on Fetus and Newborn. (2016). Umbilical cord care in the newborn infant. *Pediatrics, 138*, e20162149–e20162149. doi:10.1542/peds.2016-2149

Suddaby, E. C., Barnett, S., & Facteau, L. (2005). Skin breakdown in acute care pediatrics. *Pediatric Nursing, 31*(2), 132–138, 148.

Tansirikongkol, A., Visscher, M. O., & Wickett, R. R. (2007). Water-handling properties of vernix caseosa and a synthetic analogue. *Journal of Cosmetic Science, 58*(6), 651–662. doi:10.1111/j.1468-2494.2008.00444_5.x

Telofski, L., Morello, A., Mack Correa, M., & Stamatas, G. (2012). The infant skin barrier: Can we preserve, protect, and enhance the barrier? *Dermatology Research and Practice, 2012*, 198789. doi:10.1155/2012/198789

Tenenhaus, M., Greenberg, M., & Potenza, B. (2014). Dehydrated human amnion/chorion membrane for the treatment of severe skin and tissue loss in an preterm infant: A case report. *Journal of Wound Care, 23*, 492–495. doi:10.12968/jowc.2014.23.10.490

Thigpen, J. L. (2007). Peripheral intravenous extravasation: Nursing procedure for initial treatment. *Neonatal Network, 26*(6), 379–384. doi:10.1891/0730-0832.26.6.379

Tofani, B. F., Rineair, S. A., Gosdin, C. H., Pilcher, P. M., McGee, S., Varadarajan, K. R., & Schoettker, P. J. (2012). Quality improvement project to reduce infiltration and extravasation events in a pediatric hospital. *Journal of Pediatric Nursing, 27*, 682–689. doi:10.1016/j.pedn.2012.01.005

Tollin, M., Bergsson, G., Kai-Larsen, Y., Lengqvist, J., Sjovall, J., Griffiths, W., . . . Agerberth, B. (2005). Vernix caseosa as a multi-component defence system based on polypeptides, lipids and their interactions. *Cellular and Molecular Life Sciences, 62*(19–20), 2390–2399. doi:10.1007/s00018-005-5260-7

Treadwell, T. (2012). The management of intravenous infiltration injuries in infants and children. *Ostomy Wound Management, 58*(7), 40, 44. Retrieved from https://www.o-wm.com/article/management-intravenous-infiltration-injuries-infants-and-children

Tremaine, A. M., Armstrong, J., Huang, Y. C., Elkeeb, L., Ortiz, A., Harris, R., . . . Kelly, K. M. (2012). Enhanced port-wine stain lightening achieved with combined treatment of selective photothermolysis and imiquimod. *Journal of the American Academy of Dermatology, 66*(4), 634–641. doi:10.1016/j.jaad.2011.11.958

Visscher, M. O., Adam, R., Brink, S., & Odio, M. (2015). Newborn infant skin: Physiology, development, and care. *Clinics in Dermatology, 33*, 271–280. doi:10.1016/j.clindermatol.2014.12.003

Visscher, M. O., Chatterjee, R., Ebel, J. P., LaRuffa, A. A., & Hoath, S. B. (2002). Biomedical assessment and instrumental evaluation of healthy infant skin. *Pediatric Dermatology, 19*(6), 473–481. doi:10.1046/j.1525-1470.2002.00214.x

Visscher, M. O., Chatterjee, R., Munson, K. A., Pickens, W. L., & Hoath, S. B. (2000). Changes in diapered and nondiapered infant skin over the first month of life. *Pediatric Dermatology, 17*(1), 45–51. doi:10.1046/j.1525-1470.2000.01711.x

Visscher, M. O., deCastro, M. V., Combs, L., Perkins, L., Winer, J., Schwegman, N., . . . Bondurant, P. (2009). Effect of chlorhexidine gluconate on the skin integrity at PICC line sites. *Journal of Perinatology, 29*, 802–807. doi:10.1038/jp.2009.116

Visscher, M. O., & Narendran, V. (2014). Vernix caseosa: Formation and functions. *Newborn and Infant Nursing Reviews, 14*, 142–146. doi:10.1053/j.nainr.2014.10.005

Visscher, M. O., Narendran, V., Pickens, W. L., LaRuffa, A. A., Meinzen-Derr, J., Allen, K., & Hoath, S. B. (2005). Vernix caseosa in neonatal adaptation. *Journal of Perinatology, 25*(7), 440–446. doi:10.1038/sj.jp.7211305

Visscher, M. O., Odio, M., Taylor, T., White, T., Sargent, S., Sluder, L., . . . Bondurant, P. (2009). Skin care in the NICU patient: Effects of wipes versus cloth and water on stratum corneum integrity. *Neonatology, 96*(4), 226–234. doi:10.1159/000215593

Visscher, M. O., Utturkar, R., Pickens, W. L., LaRuffa, A. A., Robinson, M., Wickett, R. R., . . . Hoath, S. B. (2011). Neonatal skin maturation—Vernix caseosa and free amino acids. *Pediatric Dermatology, 28*(2), 122–132. doi:10.1111/j.1525-1470.2011.01309.x

Vohra, S., Roberts, R. S., Zhang, B., Janes, M., & Schmidt, B. (2004). Heat loss prevention (help) in the delivery room: A randomized controlled trial of polyethylene occlusive skin wrapping in very preterm infants. *Journal of Pediatrics, 145*(6), 750–753. doi:10.1016/j.jpeds.2004.07.036

Watterson, K., Hauck, M. J., Auker, A., Burns, R., Greider, J., Marlin, M., . . . Fenimore, E. (2018). S.T.I.C.K.: A quality improvement pediatric IV infiltration prevention bundle. *Journal of Pediatric Nursing, 41*, 38–41. doi:10.1016/j.pedn.2018.01.003

Webster, J., & McCosker, H. (1994). Cardiac monitoring in the neonatal intensive care unit: An evaluation of electrodes. *Neonatal Network, 13*(2), 51–54.

Weinstein, S. (2007). Pediatric intravenous therapy. In S. M. Weinstein (Ed.), *Plumer's principles & practice of intravenous therapy* (8th ed., p. 647). Philadelphia, PA: Lippincott Williams & Wilkins.

Wilder, K. A., Kuehn, S. C., & Moore, J. E. (2014). Peripheral intravenous and central catheter algorithm: A proactive quality initiative. *Advances in Neonatal Care, 14*, E3–E7. doi:10.1097/ANC.0000000000000125

Williams, M. L. (2008). Skin of the premature infant. In L. A. Eichenfield, I. J. Frieden, & N. B. Esterly (Eds.), *Neonatal dermatology* (2nd ed., pp. 45–58). Philadelphia, PA: Saunders Elsevier.

Wilson, J. R., Mills, J. G., Prather, I. D., & Dimitrijevich, S. D. (2005). A toxicity index of skin and wound cleansers used on in vitro fibroblasts and keratinocytes. *Advances in Skin & Wound Care, 18*, 373–378. doi:10.1097/00129334-200509000-00011

World Health Organization. (2015). *Pregnancy, childbirth, postpartum and newborn care: A guide for essential practice* (3rd ed.). Geneva, Switzerland: Author.

Yoshio, H., Lagercrantz, H., Gudmundsson, G. H., & Agerberth, B. (2004). First line of defense in early human life. *Seminars Perinatology, 28*(4), 304–311. doi:10.1053/j.semperi.2004.08.008

Yosipovitch, G., Maayan-Metzger, A., Merlob, P., & Sirota, L. (2000). Skin barrier properties in different body areas in neonates. *Pediatrics, 106*, 105–108. doi:10.1542/peds.106.1.105

Zillmer, R., Agren, M. S., Gottrup, F., & Karlsmark, T. (2006). Biophysical effects of repetitive removal of adhesive dressings on peri-ulcer skin. *Journal of Wound Care, 15*, 187–191. doi:10.12968/jowc.2006.15.5.26907

Zupan, J., & Garner, P. (2000). Topical umbilical cord care at birth. *The Cochrane Database of Systematic Reviews,* (2), CD001057. doi:10.1002/14651858.CD001057

CHAPTER 13

Hematologic System

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INTRODUCTION

The hematologic system is probably one of the least understood body systems of the neonate by the neonatal nurse. To provide the utmost care to the neonate, a thorough and complete understanding of the hematologic system and its components is necessary. The knowledge of how the blood cells develop and function as well as how the hemostatic system functions is essential in understanding the diseases of the newborn that affect the hematologic system. Without this knowledge the nurse will miss many of the subtle signs and symptoms that indicate that a problem has arisen. This chapter discusses the hematologic and hemostatic systems, as well as the most common hematologic diseases of the newborn period.

OVERVIEW OF THE HEMATOLOGIC SYSTEM

Hematopoiesis

The hematopoietic system is characterized by the presence of pluripotent stem cells that differentiate into the three types of circulating blood cells: red blood cells (RBCs), white blood cells (WBCs), and thrombocytes (platelets). The formation, production, and maintenance of blood cells are referred to as hematopoiesis. Hematopoiesis is a continuous process that involves cell maturation and destruction concurrent with new cell production. Gestational age and postnatal age influence maturation and govern individual cell components, the level of activity, and the site of production.

The liver becomes the main site for hematopoiesis beginning at approximately 5 to 6 weeks' gestation. The production peaks at 4 to 5 months of age, then slowly regresses, with the bone marrow predominating from 22 weeks' gestation on. Also helping with hematopoiesis during the fetal period are extramedullary sites of the spleen, lymph nodes, thymus, and kidneys while the long bones are small (Yoshimoto & Yoder, 2017).

Red Blood Cells

Erythropoiesis, the production of RBCs, begins at approximately 3 to 4 weeks' gestation. The RBCs are initially primitive megaloblasts, but when the liver becomes the primary site of hematopoiesis, a definitive line of RBCs is formed from the normoblasts, which progress through several phases of refinement and accrue hemoglobin before reaching maturation. When the hemoglobin concentration of the normoblast reaches 34%, the nucleus is extruded and the cell becomes a reticulocyte. Approximately 1 to 2 days later, the reticulocyte becomes a mature RBC and is released into the bloodstream. The development of the RBC is identical in the bone marrow when it becomes the primary site of erythrocyte production.

The role of the RBC is to exchange oxygen and carbon dioxide between the lungs and tissues. Tissue oxygenation occurs by hemoglobin transport, whereas carbon dioxide removal is a reaction with carbonic anhydrase. RBCs also serve as a buffer to maintain acid–base balance.

The life span of fetal and newborn RBCs is much shorter than the adult RBC life span of 120 days. The term newborn's erythrocyte can last 60 to 90 days, and that of a preterm infant, 35 to 50 days. One theoretical reason for this is the diminished deformability of the neonatal erythrocyte. Because of its larger size and cylindrical shape, the neonatal erythrocyte is more prone to destruction in the narrow sinusoids of the spleen (Gallagher, 2015; Ohls, 2017).

The mean RBC count in the term newborn is in the range of 5.8 million/mL, with an elevated reticulocyte count of 3% to 7% during the first 24 to 48 hours of life. Mean RBC counts in the premature infant range from 4.6 to 5.3 million/mL, with a greater number of circulating immature RBCs reflected in a higher reticulocyte count of 6% to 12% (Gallagher, 2015). In both groups of infants, the reticulocyte count falls abruptly to about 0% to 1% and the erythropoietin level drops to low, often undetectable, levels by the first week of life (Gallagher, 2015).

Hemoglobin

At 10 weeks' gestation, hemoglobin synthesis changes from the embryonic to the fetal form (hemoglobin F). This event coincides with the transition of the site of erythropoiesis from the yolk sac to the fetal liver. The mechanism by which stem cells and progenitor cells perform this is controlled by chromosome 11 in the beta-globin gene cluster where they are controlled by the beta-globin locus control region (LCR). The LCR controls the transcription factors to regulate the development of embryonic to fetal to adult hemoglobin (Antoniani, Romano, & Miccio, 2017). Although low levels of a third form of hemoglobin, adult hemoglobin (hemoglobin A), are detectable at this time, hemoglobin F remains the predominant form during fetal development. At 30 weeks' gestation, 90% to 100% of hemoglobin is the fetal form; the remainder is hemoglobin A. Between 30 and 32 weeks,

the percentage of hemoglobin F starts to decline. At 40 weeks, 50% to 75% of RBCs contain fetal hemoglobin; at 6 months of age, 5% to 8%; and at 1 year of age, 1%.

Each type of hemoglobin has properties that make it valuable at the time of its synthesis. Each has a different affinity for oxygen that varies its uptake and release to the tissue (Figure 13.1). Fetal hemoglobin has a high affinity for oxygen, binding it more readily at the intervillous spaces in the placenta when the fetal partial pressure of oxygen (Po_2) averages between 25 and 35 mmHg. Adult hemoglobin has a decreased affinity for oxygen, which allows easier release of oxygen to the tissues when metabolic needs are high and the lungs are functional.

Erythropoietin

The single most important factor in regulating RBC production is tissue oxygenation. The main stimulus for RBC production at times of low oxygen is the hormone erythropoietin. This circulating glycoprotein hormone, the gene of which is located on the seventh chromosome, is an obligate growth factor that stimulates stem cells to become committed progenitors of the erythrocyte (Figure 13.2). In adults, the kidneys produce 90% to 95% of erythropoietin, but in the fetus the liver is considered the predominant site of production throughout most of gestation.

The major stimulus for erythropoietin release is diminished tissue oxygenation. In the absence of erythropoietin, hypoxia has no effect on the production of RBCs. However, if erythropoietin production is intact, hypoxia stimulates a rapid increase in erythropoietin levels, which remain elevated until hypoxia no longer exists. Although the liver is less responsive to hypoxia than the kidneys, production of erythropoietin in the fetus and newborn increases within minutes to hours after a precipitating event such as hypoxia. Erythropoietin acts by directly stimulating the RBC precursors, accelerating their passage through the various maturational stages. Although erythropoietin levels increase rapidly, no change in the number of erythrocytes is noted for approximately 5 days after a hypoxic stress. When erythropoietin stimulates production of excess RBCs, the RBCs are released into the circulation before they have reached maturity (i.e., as reticulocytes); this is reflected in an elevated reticulocyte count.

Factors besides hypoxia that increase erythropoietin production in the newborn are maternal hypoxemia, smallness for gestational age, and poor placental function. Erythropoietin levels are also increased by testosterone, estrogen, thyroid hormone, prostaglandins, and lipoproteins. Cord-blood levels are normally elevated compared with adult values but drop dramatically to almost undetectable levels in the newborn. The healthy newborn, therefore, produces few RBCs in the first few weeks of life because the hypoxic stimuli of low fetal Po_2 levels are no longer present. Erythropoietin levels do not increase in the term infant until 8 to 10 weeks of age, when tissue hypoxia caused by anemia is sensed by the kidneys.

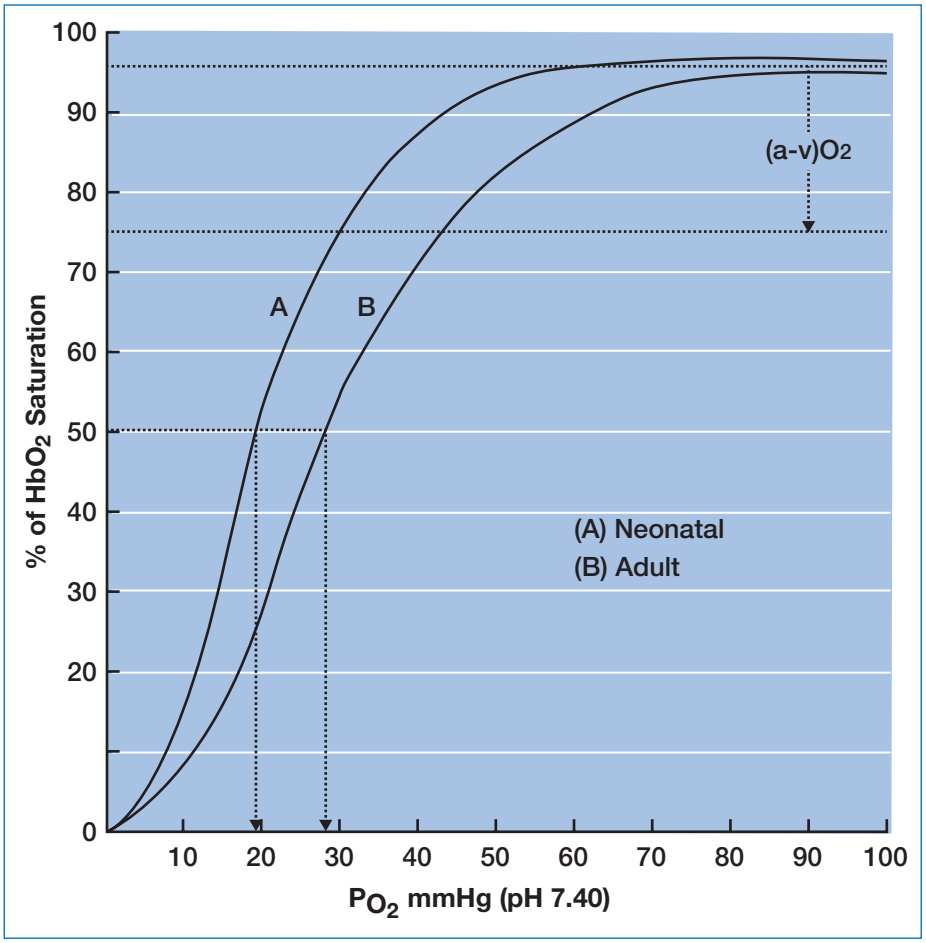


FIGURE 13.1 The affinity for oxygen (i.e., the ability of the hemoglobin molecule to bind and hold the oxygen molecule) is markedly different between fetal and adult hemoglobin. Fetal hemoglobin has a greater affinity for oxygen. It is able to bind to oxygen more readily at the intervillous spaces of the placenta, a property that is useful in the low partial pressure of oxygen (Po_2) environment of the fetus. Adult hemoglobin has a diminished affinity for oxygen, which allows easier release of oxygen to the tissue when metabolic needs are higher than those that arise in the fetus.

Source: Adapted from Sacks, L., & Delivoria-Papadopoulos, M. (1984). Hemoglobin–oxygen interactions. *Seminars in Perinatology, 8*, 168–183.

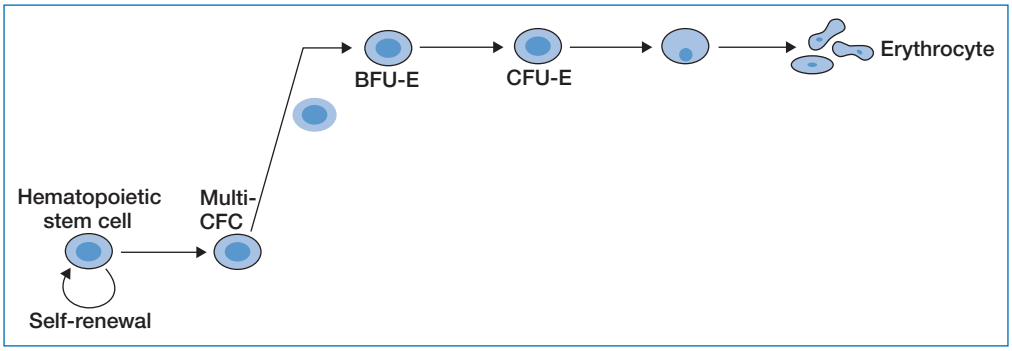


FIGURE 13.2 Hematopoietic stem cells stimulated to become erythrocytes initially develop into multipotent colony-forming cells (multi-CFC). A portion of the multi-CFC become erythroid progenitor cells, the early and late erythroid burst-forming units (BFU-E), which eventually differentiate into erythroid colony-forming units (CFU-E). These progenitor cells progress to form the normoblast, the erythrocyte precursor. Multiple divisions and alterations of the normoblast lead to the development of the reticulocyte. When the reticulocyte extrudes its nucleus, it normally moves out of the predominant production sites (i.e., the liver or bone marrow) and into the blood.

Source: Adapted from Diab, Y., & Luchtman-Jones, L. (2015). Hematologic and oncologic problems in the fetus and neonate. In R. J. Martin, A. A. Fanaroff, & M. C. Walsh (Eds.), *Fanaroff and Martin's neonatal-perinatal medicine: Diseases of the fetus and infant* (10th ed., pp. 1294–1343). Philadelphia, PA: Elsevier.

The characteristics of the neonatal erythrocyte predispose both preterm and term infants to problems associated with hemolysis and immature hepatic response to erythrocyte destruction, as well as to the effects of shortened erythrocyte life span (as is seen in physiologic neonatal anemia and anemia of the premature infant). In addition to maturational influences, preexisting maternal diseases and intrauterine abnormalities can impair RBC function and production, resulting in increased oxygen and nutritional requirements for the growing fetus (Ohls, 2017).

White Blood Cells

The formation of the WBCs begins in the liver at approximately 5 to 7 weeks' gestation and then in the lymph nodes at 12 weeks' gestation, with the number of circulating WBCs increasing dramatically during the third trimester. The purpose of the WBC is to work against foreign proteins found in the body. The production and function of WBCs are also affected by gestational age; this subject is covered in more detail in Chapter 11, Immune System.

Platelets

The production of platelets and clotting factors is also a function of gestational age. Although some factors are deficient at birth, several clotting factors and platelets are present in concentrations similar to adult levels. However, many of these components are functionally different from those of adults, possibly because of impaired activity or limited ability to respond to heightened needs. Coagulation dysfunction in the newborn may also be the result of genetic abnormalities (e.g., X-linked hemophilia), preexisting maternal illness (e.g., immune thrombocytopenic purpura), or infection (e.g., disseminated intravascular coagulation [DIC]).

Platelet counts in the newborn do not vary much in relation to gestational age. Counts are similar from 27 to 40 weeks' gestation, with the range of normal falling between 215,000 and 378,000/mm^3. At 32 weeks' gestation, platelet levels are comparable to those of an adult, but platelet function is not. Platelet counts under 150,000/mm^3 are considered thrombocytopenic.

Blood Volume

Normal blood values found shortly after birth reflect a time of maximum change. Blood values at birth depend on (a) the timing of cord clamping, (b) the infant's gestational age, (c) the blood sampling site, and (d) the technique used to obtain adequate blood flow.

The timing of cord clamping and the positional differences between the infant and the placenta can significantly influence newborn blood volume. Complete emptying of placental vessels before clamping can increase blood volume by 61%; one quarter of the placental transfusion occurs within the first 15 seconds, and half of the transfusion is complete by 1 minute. In previous editions of this text, delayed cord clamping (DCC) was considered controversial due to some perceived negative effect on the neonate, but over time randomized controlled trial studies have been done in both term and preterm neonates to dispel those thoughts. The results of the studies on DCC for greater than 30 seconds in vigorous term and preterm newborns that have an intact placental circulation have been shown to be advantageous to the newborn, both preterm and term. Preterm newborns who had DCC for 30 to 60 seconds had higher blood pressure, higher blood volume resulting in higher hematocrits (Hct), decreased need for blood transfusion, higher ferritin levels resulting in lower incidence of iron deficiency, lower incidence of neonatal anemia, and decreased incidence of intraventricular hemorrhages and necrotizing enterocolitis (American Academy of Pediatrics [AAP], 2017; American College of Obstetricians and Gynecologists [ACOG] Committee on Obstetric Practice, 2017). For the term neonate, the advantages are increased hemoglobin levels at birth and improved iron stores, which may lead to less incidence of iron deficiency anemia. The one concern with DCC is that it may also increase the amount and severity of jaundice in term neonates, so it is essential to ensure that the neonate is observed for signs of jaundice and has adequate follow-up (AAP, 2017; AAP & ACOG, 2017; ACOG Committee on Obstetric Practice, 2017). For these reasons both ACOG (Committee on Obstetric Practice, 2017) and AAP (2017) recommend DCC for all neonates that are vigorous at birth for 30 to 60 seconds, when the mother is hemodynamically stable.

Umbilical cord milking (UCM) is another manner to increase blood volume in neonates, but UCM has not been studied as rigorously as DCC. UCM can be done in 10 to 15 seconds versus the 30 to 60 seconds required for DCC and could be beneficial in cases when there is a need for immediate resuscitation. While the studies done on DCC show similar results, those on UCM show varied results, making it hard to generalize the results. At this point there is not strong enough evidence to recommend UCM in either term or preterm neonates (Al-Wassia & Shah, 2015).

TABLE 13.1

AGE-SPECIFIC NORMAL BLOOD CELL VALUES IN FETAL SAMPLES (26–30 WEEKS' GESTATION) AND NEONATAL SAMPLES (28–44 WEEKS' GESTATION)

Age	Hb (g/dL)[a]	Hct (%)[a]	MCV (fL)[a]	MCHC (g/dL RBC)[a]	Reticulocytes	WBCs ($\times 10^3$/mL)[b]	Platelets (10^3/mL)[b]
26–30 weeks' gestation[c]	13.4 (11)	41.5 (34.9)	118.2 (106.7)	37.9 (30.6)	–	4.4 (2.7)	254 (180–327)
28 weeks	14.5	45	120	31.0	(5–10)	–	275
32 weeks	15.0	47	118	32.0	(3–10)	–	290
Term[d] (cord)	16.5 (13.5)	51 (42)	108 (98)	33.0 (30.0)	(3–7)	18.1(9–30)[d]	290
1–3 days	18.5 (14.5)	56 (45)	108 (95)	33.0 (29.0)	(1.8–4.6)	18.9 (9.4–34)	192
2 weeks	16.6 (13.4)	53 (41)	105 (88)	31.4 (28.1)	–	11.4 (5–20)	252
1 month	13.9 (10.7)	44 (33)	101 (91)	31.8 (28.1)	(0.1–1.7)	10.8 (4–19.5)	–

[a] Data are mean (number in parenthesis is −2 standard deviations [SD]).

[b] Data are mean (number in parenthesis is −2 SD).

[c] In infants younger than 1 month, capillary Hb exceeds venous Hb: at 1 hour old, the difference is 3.6 g; at 5 days, 2.2 g; at 3 weeks, 1.1 g.

[d] Mean (95% confidence limits).

Hb, Hemoglobin; Hct, hematocrit; MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration; WBCs, white blood cells.

Source: Modified from Costa, K. (2018). Hematology. In *The Harriet Lane handbook* (pp. 364–394). Philadelphia, PA: Elsevier.

The average blood volume of the neonate without DCC is approximately 85 mL/kg of body weight in the term infant, though it can be as high as 90 to 105 mL/kg in the preterm infant. As stated earlier, DCC can increase the blood volume by 61%, thus making term infant blood volume as high as 136 mL/kg and the preterm infant blood volume as high as 150 mL/kg. The younger the infant's gestational age, the greater the blood volume will be per kilogram of body weight as a result of a higher plasma volume.

The hemoglobin concentration and Hct are also functions of gestational age, especially in infants born before 32 weeks' gestation. The average mean hemoglobin concentration at 26 to 30 weeks is 13.4 g/dL, with an average mean Hct of 41.5%. In the term infant, mean hemoglobin values range from 16 to 17 g/dL, with mean Hct values between 51% and 60% (Gallagher, 2015). Mean hemoglobin values in postmature infants are higher than in the term infant, possibly as a result of progressive placental dysfunction and oxygen deficit, which stimulates the release of erythropoietin. Table 13.1 summarizes the differences in hematologic values as a function of increasing gestational and postnatal age.

It is important to consider the sampling site and the quality of blood flow when interpreting laboratory values. The hemoglobin levels of capillary blood are 10% to 20% higher than those of venous and arterial blood. This discrepancy can be minimized by warming the extremity before drawing blood to enhance peripheral perfusion, allowing better spontaneous blood flow. Discarding the first few drops obtained on a capillary draw also improves the accuracy of the sample. Sampling by the venous route also requires care; poor blood flow through small-bore needles increases the chance of hemolysis, which can lead to sampling errors. Greater accuracy can be obtained by using the largest possible bore needle and removing the needle from the syringe before placing the sample in the specimen container. Gestational age also affects the discrepancy between reported capillary and venous results: the younger the gestational age, the larger the discrepancy. The key to accuracy in hematology laboratory values lies in the use of a consistent sampling site.

Blood Group Type

The RBCs have antigens located on the surface of the cell membranes that can cause antigen–antibody reactions. Blood is classified by groups and types based on the antigens that are found on the RBC. The four major blood types are A, B, O, and AB. The most common blood types in the population are O at 47% and A at 41% (Hall, 2016). Antibodies to the antigens of different blood types occur naturally in the plasma (Table 13.2). For example, type A blood has A antigens on the cell surface but has circulating anti-B antibodies in the plasma. Type B blood has just the opposite, B antigens on the cell surface and anti-A antibodies in the plasma. Type AB blood has A and B antigens on the cell surface and neither antibody in the plasma, and type O blood has neither antigen on the cell surface and both anti-A and anti-B antibodies in the plasma. Antigens are usually polypeptides and complex proteins; antibodies are immunoglobulins (mostly IgG and IgM).

The other type of antigen is Rh antigens. Chromosome 1 stores the genetic material governing Rh antigens, and in most individuals two genes, *CD240CE* and *CD240D*, determine the Rh blood group (Liley, Gardner, Lopriore, & Smits-Wintjens, 2015). There are three presumed Rh gene loci with the capability of producing five recognized antigens in the Rh complex: C, D, E, c, d, and e. Each individual has a paired set of these factors, having inherited a single set of C or c, D or d, and E or e from each parent. A predilection exists toward three particular combinations, two Rh positive (CDe and cDE) and one Rh negative (cde). Of these six factors, the two involved in Rh determination are D and d. The D antigen is most prevalent; its presence on the RBC indicates an Rh-positive cell, whereas its absence indicates an Rh-negative cell. Approximately 85% of Caucasians are Rh positive and 15% Rh negative. African Americans are approximately 95% Rh positive, and Africans are virtually 100% Rh positive (Hall, 2016). Because of single-set inheritance from each parent, the potential exists for three different combinations of paired antigens: one pair being both d (Rh negative, homozygous), another pair being both D (Rh positive, homozygous), and the third pair being a combination of d and D (Rh positive, heterozygous). The end product is the production or absence of Rh antigen positioned on the surface of the RBC. The Rh antigen can be detected as early as 38 days' gestation on the fetal RBC and attains complete development during fetal life. This antigen is necessary for normal function of the RBC membrane, and, unlike A and B antigens, which can be found in other tissues, it is confined exclusively to the RBC. Antibodies never occur naturally in the Rh system; exposure to the antigen is necessary to produce antibodies.

TABLE 13.2

BLOOD GROUPS AND THEIR ANTIGENS AND ANTIBODIES

Blood Group Type	Antigens	Antibodies
O	None	Anti-A, Anti-B
A	A	Anti-B
B	B	Anti-A
AB	A and B	None

Source: Adapted from Hall, J. E. (2016). *Guyton and Hall textbook of medical physiology* (13th ed.). Philadelphia, PA: Elsevier..

Hemostatic System

The components involved in blood coagulation and fibrinolysis (dissolution of a formed clot) are produced in the liver, vascular wall, and tissue during early fetal life. Many of the clotting factors (procoagulants) and anticoagulants (inhibitors) can be identified during the 8th to 12th week of gestation. However, procoagulants, anticoagulants, and the substances responsible for dissolution of a clot, fibrinolytics, do not increase in number and function or reach adult levels simultaneously (Tables 13.3–13.5). Some components increase with increasing gestational age, whereas others achieve normal adult levels several weeks to months before the fetus reaches term. Still other components do not achieve normal adult levels until several weeks to months after birth. Although the function of coagulation factors and anticoagulants in the fetus is not identical to that in an older child or adult, initial vascular response to injury by release of tissue thromboplastin is functional in the fetus as early as 8 weeks.

Hemostasis consists of a delicate and dynamic balance between factors that prevent exsanguination and those that keep the blood in a fluid form. The balanced interrelationship among four distinct components ensures orderly hemostasis and fibrinolysis when vascular integrity is destroyed or interrupted. The four constituents are vascular spasm, platelets and their activating substances, coagulation or plasma factors, and the fibrinolytic pathway.

TABLE 13.3

NORMAL COAGULATION TEST RESULTS AND BLOOD LEVELS OF COAGULATION FACTORS IN THE FETUS (19–27 WEEKS' GESTATION) AND NEWBORN (28 WEEKS' GESTATION TO TERM)

Test/Factor	19–27 Weeks Mean ± SD	28–31 Weeks Mean (boundary)	30–36 Weeks, Day 1 Mean (boundary)	30–36 Weeks, Day 5 Mean (boundary)	Full Term, Day 1 Mean (boundary)	Full Term, Day 5 Mean (boundary)
Test						
Prothrombin time (seconds)	–	15.4 (14.6–16.9)	13 (10.6–16.2)	12.5 (10–15.3)	13 (10.1–15.9)	12.4 (10–15.3)
Activated partial thromboplastin time (seconds)	–	108 (80–168)	53.6 (27.5–79.4)	50.5 (26.9–74.1)	42.9 (31.3–54.5)	42.6 (25.4–59.8)
Thrombin clotting time (seconds)	–	–	24.8 (19.2–30.4)	24.1 (18.8–29.4)	23.5 (19–28.3)	23.1 (18–29.2)
Factor						
Fibrinogen (g/L)	1 ± 0.4	2.56 (1.6–5.5)	2.43 (1.5–3.73)	2.8 (1.6–4.18)	2.83 (1.67–3.99)	3.12 (1.62–4.62)
Factor II (U/mL)	0.12 ± 0.02	0.31 (0.19–0.54)	0.45 (0.2–0.77)	0.57 (0.29–0.85)	0.48 (0.26–0.7)	0.63 (0.33–0.93)
Factor V (U/mL)	0.41 ± 0.1	0.65 (0.43–0.8)	0.88 (0.41–1.44)	1 (0.46–1.54)	0.72 (0.34–1.08)	0.95 (0.45–1.45)
Factor VII (U/mL)	0.28 ± 0.04	0.37 (0.24–0.76)	0.67 (0.21–1.13)	0.84 (0.3–1.38)	0.66 (0.28–1.04)	0.89 (0.35–1.43)
Factor VIII (U/mL)	0.39 ± 0.14	0.79 (0.37–1.26)	1.11 (0.5–2.13)	1.15 (0.53–2.05)	1 (0.5–1.78)	0.88 (0.5–1.54)
von Willebrand factor (U/mL)	0.64 ± 0.13	1.41 (0.83–2.23)	1.36 (0.78–2.1)	1.33 (0.72–2.19)	1.53 (0.5–2.87)	1.4 (0.5–2.54)
Factor IX (U/mL)	0.1 ± 0.01	0.18 (0.17–0.2)	0.35 (0.19–0.65)	0.42 (0.14–0.74)	0.53 (0.15–0.91)	0.53 (0.15–0.91)
Factor X (U/mL)	0.21 ± 0.03	0.36 (0.25–0.64)	0.41 (0.11–0.71)	0.51 (0.19–0.83)	0.4 (0.12–0.68)	0.49 (0.19–0.79)
Factor XI (U/mL)	–	0.23 (0.11–0.33)	0.3 (0.08–0.52)	0.41 (0.13–0.69)	0.38 (0.1–0.66)	0.55 (0.23–0.87)
Factor XII (U/ml)	0.22 ± 0.03	0.25 (0.05–0.35)	0.38 (0.1–0.66)	0.39 (0.09–0.69)	0.53 (0.13–0.93)	0.47 (0.11–0.83)
Prekallikrein (U/mL)	–	0.26 (0.15–0.32)	0.33 (0.09–0.57)	0.45 (0.26–0.75)	0.37 (0.18–0.69)	0.48 (0.2–0.76)
High-molecular-weight kininogen (U/mL)	–	0.32 (0.19–0.52)	0.49 (0.09–0.89)	0.62 (0.24–1)	0.54 (0.06–1.02)	0.74 (0.16–1.32)
Factor XIIIa (U/mL)	–	–	0.7 (0.32–1.08)	1.01 (0.57–1.45)	0.79 (0.27–1.31)	0.94 (0.44–1.44)
Factor XIIIb (U/mL)	–	–	0.81 (0.35–1.27)	1.1 (0.68–1.58)	0.76 (0.3–1.22)	1.06 (0.32–1.8)
Plasminogen (U/mL)	–	–	1.7 (1.12–2.48)	1.91 (1.21–2.61)	1.95 0.35 (44)	2.17 ± 0.38 (60)

SD, standard deviation.

Source: Modified from Andrew, M., Paes, B., & Johnston, M. (1990). Development of the hemostatic system in the neonate and young infant. *American Journal of Pediatric Hematology/Oncology, 12*, 97–98. doi:10.1097/00043426-199021000-00019

TABLE 13.4

NORMAL BLOOD LEVELS OF COAGULATION INHIBITORS IN NEWBORNS (30 WEEKS' GESTATION TO TERM)

Coagulation Inhibitors	30–36 Weeks' Gestation		Full Term	
	Day 1 Mean (boundary)	Day 5 Mean (boundary)	Day 1 Mean (boundary)	Day 5 Mean (boundary)
Antithrombin III (U/mL)	0.38 (0.14–0.62)	0.56 (0.3–0.82)	0.63 (0.39–0.87)	0.67 (0.41–0.93)
Alpha2-macroglobulin (U/mL)	1.1 (0.56–1.82)	1.25 (0.71–1.77)	1.39 (0.95–1.83)	1.48 (0.98–1.98)
C1 esterase inhibitor (U/mL)	0.65 (0.31–0.99)	0.83 (0.45–1.21)	0.72 (0.36–1.08)	0.90 (0.6–1.2)
Alpha1-antitrypsin (U/mL)	0.9 (0.36–1.44)	0.94 (0.42–1.46)	0.93 (0.49–1.37)	0.89 (0.49–1.29)
Heparin cofactor II (U/mL)	0.32 (0.1–0.6)	0.34 (0.1–0.69)	0.43 (0.1–0.93)	0.48 (0.1–0.96)
Protein C (U/mL)	0.28 (0.12–0.44)	0.31 (0.11–0.51)	0.35 (0.17–0.53)	0.42 (0.2–0.64)
Protein S (U/mL)	0.26 (0.14–0.38)	0.37 (0.13–0.61)	0.36 (0.12–0.6)	0.5 (0.22–0.78)

Source: Modified from Andrew, M., Paes, B., & Johnston, M. (1990). Development of the hemostatic system in the neonate and young infant. *American Journal of Pediatric Hematology/Oncology, 12*, 97–98. doi:10.1097/00043426-199021000-00019

TABLE 13.5

NORMAL BLOOD LEVELS OF FIBRINOLYTIC COMPONENTS IN PREMATURE AND TERM NEWBORNS

Fibrinolytic Component	Premature Infants		Full-Term Infants	
	Day 1 Mean (boundary)	Day 5 Mean (boundary)	Day 1 Mean (boundary)	Day 5 Mean (boundary)
Plasminogen (U/mL)	1.7 (1.12–2.48)	1.91 (1.21–2.61)	1.95 (1.25–2.65)	2.17 (1.41–2.93)
Tissue plasminogen activator (ng/mL)	8.48 (3–16.7)	3.97 (2–6.93)	9.6 (5–18.9)	5.6 (4–10)
Alpha2-antiplasmin (U/mL)	0.78 (0.4–1.16)	0.81 (0.49–1.13)	0.85 (0.55–1.15)	1 (0.7–1.3)
Plasminogen activator inhibitor (U/mL)	5.4 (0–12.2)	2.5 (0–7.1)	6.4 (2–15.1)	2.3 (0–8.1)

Source: Modified from Andrew, M., Paes, B., & Johnston, M. (1990). Development of the hemostatic system in the neonate and young infant. *American Journal of Pediatric Hematology/Oncology, 12*, 97–98. doi:10.1097/00043426-199021000-00019

INITIAL STEPS IN HEMOSTASIS

Vascular Spasm

Initial hemostasis in a ruptured blood vessel consists of vascular spasm, which is a consequence of multiple mediator interactions, nervous reflexes, and localized muscle spasm. Although nervous reflexes are a response to pain, most of the vascular spasm is due to muscle contraction in the vessel wall secondary to direct injury. This vascular response to injury is present in an 8-week fetus and at term is the equivalent of adult norms in regard to capillary fragility and bleeding time. This component is dependent on gestational age, as is evident in the increased capillary fragility shown by the preterm infant.

Platelet Plug Formation

The second mechanism of hemostasis after vascular injury is the formation of the platelet plug. Platelets coming into contact with an injured vascular wall adhere to the wall and form a platelet plug. This hemostatic plug is the primary means of closing small vascular holes at the capillary and small-vessel level. The platelets' ability to adhere on contact to a denuded vascular wall requires a glycoprotein, von Willebrand factor (vWF), which is synthesized by vascular endothelial cells and megakaryocyte vWF

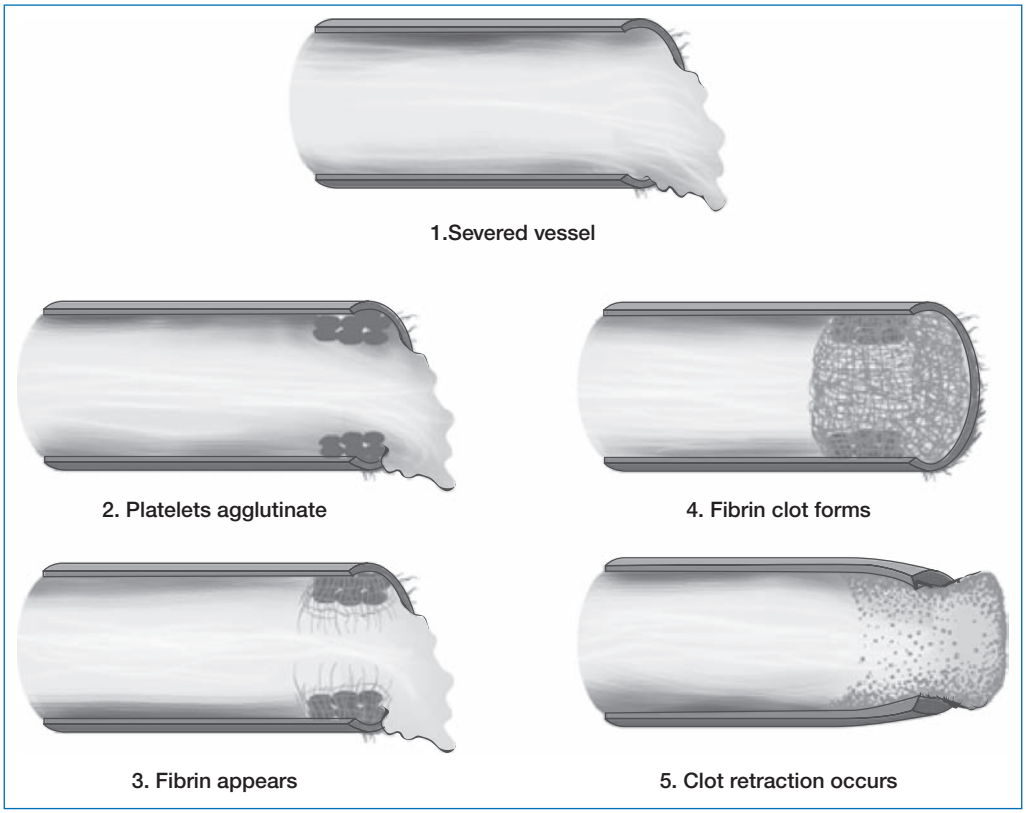


FIGURE 13.3 When vessel wall injury occurs, the initial clotting process begins with the formation of a platelet plug. Platelet activation stimulates fibrinogen receptors found on the surface of the platelets, which enhance their aggregation with other platelets and fibrinogen. The fibrin clot that forms retracts and occludes the damaged vascular wall.

Sources: Adapted from Hall, J. E. (2016). *Guyton and Hall textbook of medical physiology* (13th ed.). Philadelphia, PA: Elsevier. Witt, S. (1948). *Hemostatic agents.* Springfield, IL: Charles C. Thomas Publishers.

complexes with Factor VIII (antihemophilic factor) and both circulate jointly.

Platelets also have the ability to aggregate (stick to other platelets), forming large clumps. Aggregation is made possible by the platelet's ability to modify its shape and to secrete many biochemical substances (platelet release reaction) that enhance cohesion. When platelets and associated glycoproteins are activated by excess release of these biochemical substances during times of stress, fibrinogen receptors appear on the surface of the platelet. These receptors enhance the platelets' ability to bind fibrinogen, which in turn cross-links the platelets, allowing them to aggregate. This provides a tight mesh or clot around an injured vessel that controls bleeding (Figure 13.3). After 32 weeks' gestation, average platelet counts are comparable to those of term infants and adults, but the ability of platelets to aggregate is relatively diminished.

Coagulation

When bleeding cannot be controlled with merely a platelet plug, circulating plasma coagulation factors are triggered to form a network of fibrin that turns the existing plug into a hemostatic seal, which in turn completes hemostasis. Fibrin threads, necessary for clot formation, can develop within 15 to 20 seconds in the presence of normal coagulation factors. Within 3 to 6 minutes after vascular rupture, the entire opening is occluded by clot; within 30 to 60 minutes, the clot begins to retract, pulling the injured vascular portions together and further sealing the vascular end. This coagulation reaction involves several plasma proteins and three distinct phases. The first phase involves the formation of prothrombin activator, followed by the activation of prothrombin to thrombin (formation of thrombin), and then concludes with the conversion of soluble fibrinogen to fibrin (fibrin clot formation; Hall, 2016).

Phase I: Formation of Prothrombin Activator. According to the earliest theories on coagulation (cascade theory), prothrombin activator can be generated by two separate pathways, the intrinsic and extrinsic pathways. The intrinsic pathway is triggered by trauma or damage that occurs inside the vessel or to the blood itself and the extrinsic pathway is triggered by the production of tissue thromboplastin that is generated by vessel wall damage. This bimodal pathway can be interrupted or negated by a deficiency in platelets or any of the plasma coagulation factors or by the presence of inhibitors (anticoagulants) in the plasma. Selective activation of one of these pathways depends on the site and severity of injury.

Activation of the intrinsic pathway is slower because it lacks the major stimulus of the extrinsic pathway, tissue thromboplastin generated by vessel wall damage. The intrinsic pathway relies on blood trauma or injury within the vessel to alter platelets and plasma proteins and to convert dormant factors (zymogens), naturally found in circulating blood, into active proteolytic enzymes (Figure 13.4). Each activated enzyme subsequently reacts with the succeeding factor, changing it into its activated form. The steps of intrinsic activation of coagulation are as follows:

1. An activator (blood trauma, injury within the vessel, or contact with collagen) activates Factor XII, converting it to Factor XIIa, while simultaneously damaging platelets, which causes a release of platelet phospholipids.
2. Factor XIIa, in conjunction with prekallikrein and high-molecular-weight kininogen, activates Factor XI, converting it to Factor XIa.

3. Factor XIa activates Factor IX, converting it to Factor IXa.
4. Factor IXa, platelet phospholipid, and Factor VIII combine to activate Factor X, converting it to Factor Xa.
5. Factor Xa combines with Factor V and platelet phospholipids to form prothrombin activator (prothrombinase), which releases thrombin from prothrombin. Calcium is required for this and the preceding two steps.

The extrinsic pathway can generate thrombin in a matter of seconds when injury occurs outside the vascular space (Figure 13.5). Tissue thromboplastin (tissue factor), composed of glycoproteins and phospholipids, is produced when tissue is injured. When plasma comes in contact with this substance, the initial intrinsic phases are bypassed and the following responses occur:

1. Tissue thromboplastin or tissue factor (Factor III) activates Factor VII to Factor VIIa. These two factors form a complex with glycoprotein in the presence of ionized calcium (tissue factor–Factor VIIa complex) that activates Factor X, converting it to Factor Xa.
2. In the presence of calcium, Factor Xa forms complexes with phospholipids and Factor V to form prothrombin activator.

From this point on, the intrinsic and extrinsic pathways are identical, with both proceeding to phase II.

Phase II: Formation of Thrombin. Prothrombin activator from either of the two pathways continues the clotting cascade by further influencing the breakdown of the unstable plasma protein prothrombin. Prothrombin (Factor II) is synthesized by the liver under the influence of vitamin K, along with the other factors that form the prothrombin complex (Factors VII, IX, and X). When acted on by prothrombin activator, prothrombin forms the potent coagulant thrombin. The newly formed thrombin stimulates completion of the third and final phase of coagulation.

Phase III: Fibrin Clot Formation

Procoagulants. Thrombin promotes the conversion of fibrinogen (Factor I), a protein produced by the liver, into fibrin by splitting off two peptides from the soluble fibrinogen molecule. This exposes two sites, to which other split fibrin molecules can cross-link, forming an insoluble fibrin chain. Fibrin stabilizing factor (Factor XIII) further strengthens the tight bond of this developing fibrin mesh. Fibrin stabilizing factor is naturally found in the plasma and is also secreted by entrapped platelets. The forming fibrin clot begins to contract and retract with the help of platelets that have actin-myosin action, the same action by which a muscle works. Extension of the clot into the surrounding circulating blood promotes further thrombosis. Thrombin from the clot has the ability to cleave prothrombin into more thrombin and enhances the production of prothrombin activator, thus acting as a potent biofeedback system for perpetuation of the clotting cascade.

Anticoagulants. Throughout the entire coagulation pathway, the action of the activated enzymes is modulated at each stage by multiple and specific inhibitors (anticoagulants). Consequently, coagulation is a process of balance between coagulation factors and naturally occurring inhibitors. Some of these anticoagulants are endothelial surface factors that prevent coagulation until the vessel's endothelial wall is damaged. One such factor is the smoothness of the wall, which prevents any adherence and subsequent activation; another is the monomolecular layer of protein covering the wall, which repels plasma clotting factors and platelets.

Two inhibitors, alpha-1-antitrypsin and C1 esterase inhibitor, interfere with the coagulation factors involved in the initial activation of the intrinsic pathway, as does Factor Xa despite its role in cleaving prothrombin into thrombin. Factor Xa rapidly binds with a tissue factor pathway inhibitor (TFPI) found in the plasma. This complex, TFPI–Factor Xa, joins with the tissue factor–Factor

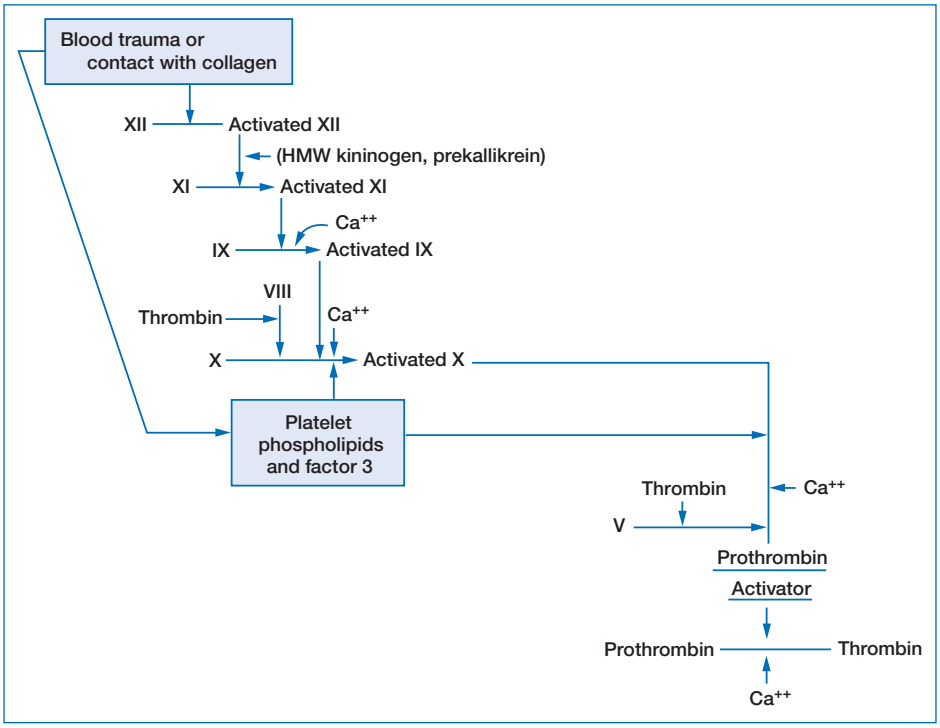


FIGURE 13.4 The intrinsic pathway for initiating the clotting cascade is activated by trauma to the blood, injury within the vessel, or contact with collagen.
HMW, high molecular weight.
Source: From Hall, J. E. (2016). *Guyton and Hall textbook of medical physiology* (13th ed.). Philadelphia, PA: Elsevier.

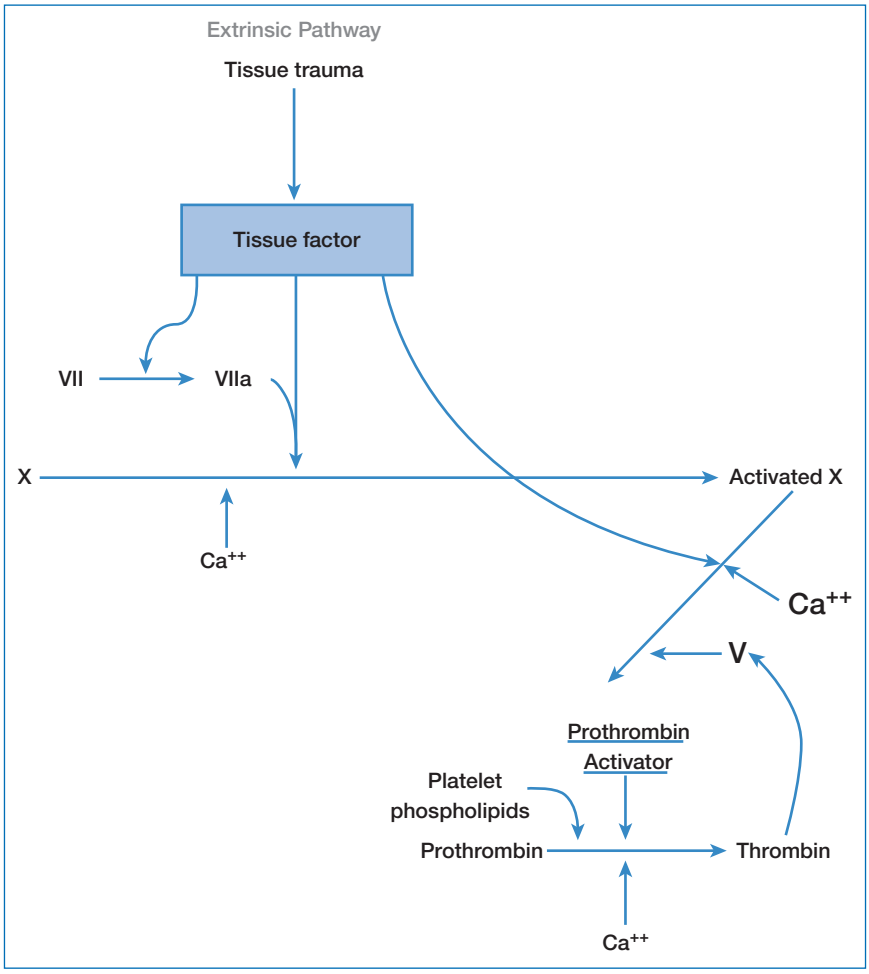


FIGURE 13.5 The extrinsic pathway for initiating the clotting cascade can generate thrombin rapidly as a result of thromboplastin release from injured tissue.

Source: Hall, J. E. (2016). *Guyton and Hall textbook of medical physiology* (13th ed.). Philadelphia, PA: Elsevier.

VIIa complex to form a quaternary complex that inhibits further activation of Factor X by tissue factor.

Thrombin also acts as its own inhibitor by stimulating activation of protein C, which inactivates Factors V and VIII in the presence of another vitamin K–dependent inhibitor, protein S. A deficiency of these two proteins has been implicated in cases of neonatal thrombosis.

Other inhibitors of thrombin formation are: (a) fibrin threads created during clot formation, which absorb thrombin, thus removing it from circulation and eliminating its potential for further coagulation; (b) thrombomodulin, found on the endothelial surfaces of the body and in the plasma complexes with thrombin, which eliminates thrombin's ability to cleave fibrinogen; (c) alpha-2-macroglobulin, which inhibits proteases, including thrombin; (d) antithrombin III, which combines with thrombin, blocking the conversion of fibrinogen into fibrin; and (e) heparin cofactor II, which removes several activated procoagulants. Both antithrombin III and heparin are produced in the precapillary connective tissue of the lungs and liver.

Fibrinolysis. Once a clot develops, it can be invaded by fibroblasts that lay down connective tissue throughout the clot or it can be dissolved. The process of dissolution occurs by activation of naturally occurring factors that lyse the clot. Fibrinolysis is activated simultaneously with stimulation of the coagulation system, with powerful but inactivated anticoagulants built right into the clot. One of these anticoagulants, plasminogen, is manufactured by the liver, kidneys, and eosinophils. Under the influence of thrombin, activated Factor XII, tissue plasminogen activator (t-PA; located on the vascular endothelium), and urokinase plasminogen activator (u-PA; found in the urine), plasminogen is converted into plasmin, a proteolytic enzyme that breaks down fibrin into fibrin split products. Plasmin not only digests the fibrin chains but also deactivates fibrinogen; Factors V, VII, and XII; and prothrombin. Plasmin can be inactivated by its inhibitor, alpha-2-antiplasmin; t-PA can be inactivated by its inhibitor, plasminogen activator inhibitor-1.

In summary, both term and preterm newborns have the ability to create a balance between transitory deficiencies in the amount and function of a variety of clotting factors, platelets, and anticoagulant factors. The homeostasis between clotting factors and anticoagulants places the newborn in a mildly hypercoagulable state at birth. Compared with older children and adults, therefore, the newborn has no greater tendency to bleed but does have several differences in regard to coagulation components and reserves, including (a) gestational age-dependent variations in the concentrations of coagulation factors, anticoagulants, and fibrinolytics; (b) a faster turnover rate of components; (c) a slower rate of synthesis of components; and (d) limited ability to supply necessary components during times of increased need (Cantor, 2015).

ASSESSMENT OF HEMATOLOGIC FUNCTION

Because infants respond to a variety of problems in a similar manner, many clinical findings (e.g., hypoglycemia, hypocalcemia, hypothermia, apnea, bradycardia, cyanosis, lethargy, poor feeding) warrant at least a complete blood count (CBC) to determine if a hematologic reason exists for these symptoms. With active bleeding, platelet counts, clotting studies, fibrinogen levels, and measurements of products of fibrinolysis (e.g., D-dimer, fibrin split products, or fibrin degradation products) can shed light on the type of blood dyscrasia present and can direct the caregiver to the appropriate therapeutic response. These studies also provide a way to monitor and evaluate treatments. However, laboratory data are most helpful when they are used in conjunction with astute observation and physical assessment skills.

Several physical findings can help determine the well-being and homeostasis of the hematologic system (Box 13.1). Cutaneous abnormalities such as hematomas, abrasions, petechiae, and bleeding should alert the nurse to the possibility of a hematologic abnormality. Hepatosplenomegaly also can indicate abnormal breakdown of RBCs. Hepatosplenomegaly concurrent with hyperbilirubinemia and hemolysis can signal alloimmune problems (e.g., Rh and ABO incompatibilities) or acquired, congenital, or postnatal infection (e.g., cytomegalovirus [CMV], toxoplasmosis, herpes simplex infection, or hepatitis).

COMMON HEMATOLOGIC DISORDERS

Blood Group Incompatibilities

Blood group incompatibilities were first recognized in the 1940s with the discovery of the Rh grouping and the first test for detection of antibody-coated RBCs, devised by Coombs in 1946. Before the introduction of Rh immune globulin (i.e., RhIgG, RhIG, RhoGAM, Rhophylac) in 1964 and its release for general use in 1968, Rh incompatibility accounted for one third of all blood group incompatibilities. With the use of RhIgG, the frequency of Rh incompatibility has dropped significantly, and ABO has become the main blood group incompatibility, with sensitization occurring in 3% of all infants. Both incompatibilities involve maternal antibody response to fetal antigen, leading to fetal RBC destruction by hemolysis. Rh antibody response is elicited on exposure to antigen and does not exist spontaneously, whereas anti-A and anti-B antibodies occur naturally. These entities also differ in the severity of the effect on the fetus and newborn and in the method of treatment.

Box 13.1

PHYSICAL FINDINGS HELPFUL IN EVALUATING THE INTEGRITY OF THE HEMATOLOGIC SYSTEM

- Ecchymosis
- Hematomas
- Hepatosplenomegaly
- Jaundice
- Obvious blood loss—hemorrhage
- Pallor
- Petechiae
- Plethora

Other minor blood groupings (e.g., Kell, C, E, Duffy, and Kidd) may also be involved in incompatibilities that result in hyperbilirubinemia, but Rh and ABO incompatibilities are the most common, accounting for 98% of all cases. There are 400 known RBC antigens that can induce antibody production. Some of these antibodies are induced after transfusion therapy with incompatible blood; others occur in response to the transfer of incompatible fetal blood cells into the maternal circulation during pregnancy. The Rh system alone has 40 discrete antigens, but only six (C, D, E, c, d, and e) are important.

ABO Incompatibility

As discussed earlier in this chapter, the four major blood types are A, B, O, and AB, with the antibodies to the antigens of different blood types occurring naturally in the plasma (Table 13.2). Antigens or agglutinogens present on the fetal RBC surface of each blood type react with antibodies or agglutinins found in the maternal plasma of opposing blood types. Of the 30 common antigens involved in antigen–antibody reactions, the ABO antigens are one of two groups most likely to be a problem, the other being the Rh group (Hall, 2016).

With antigen and antibody in harmony, no RBC destruction occurs, but when a conflicting antibody is introduced into the circulation, RBC destruction may occur. RBCs have multiple binding sites to which opposing antibodies can attach. An antibody is capable of simultaneously attaching to several RBCs, thus creating a clump of cells. This clumping of cells, known as agglutination, can cause occlusion of small vessels and impair local circulation and tissue oxygenation. Fetal RBCs coated with antibodies attract phagocytes and macrophages that eventually destroy these agglutinated RBCs, usually through hemolysis by the reticuloendothelial cells in the spleen. Hemolysis can occur without preliminary agglutination, but it is a more delayed process because the body must first activate its complement system. High antibody titers (hemolysins) are required to stimulate this system, which causes the release of proteolytic enzymes that rupture the cell membrane.

In a transfusion reaction, when opposing blood types are mixed, the donor's RBCs are agglutinated, and the recipient's blood cells tend to be protected. The plasma portion of donor blood that contains antibodies becomes diluted by the recipient's blood volume, thus reducing donor antibody titers in the recipient's circulation. However, recipient antibody titers are adequate to destroy the donor RBCs by agglutination and hemolysis or by hemolysis alone. This is the situation in ABO incompatibility. In such cases, the maternal blood type usually is O, containing anti-A and anti-B antibodies in the serum, whereas the fetus or newborn is type A or B. Although incompatibility can occur between A and B types, it is not seen as frequently as AO or BO because of the globulin composition of the antibodies. In the O-type mother, the antibodies are usually IgG and can cross the placenta, whereas the antibodies of the type A or B mother are frequently IgM, which are too large to cross the placenta.

When transplacental hemorrhage (TPH) occurs between an ABO-incompatible mother and fetus, fetal blood entering the maternal circulation undergoes agglutination and hemolysis by maternal antibodies. This rapid response prevents the development of antibodies to other antigens present on fetal RBCs, because a time lapse is required for activation of the immune system. Consequently, fetal RBCs that are Rh positive in addition to being type A or type B are destroyed by naturally occurring anti-A or anti-B antibodies before any maternal antibodies to Rh factor (anti-D) can be produced. This naturally occurring phenomenon is the basis for the use of RhIgG, in which extrinsic anti-D destroys fetal cells before the maternal immune system can be activated to produce antibodies.

Despite this destruction of fetal RBCs, maternal anti-A or anti-B antibodies of the IgG form can freely cross the placenta and adhere to RBCs in the fetal circulation. For this reason, ABO incompatibility can occur in the first pregnancy (40%–50% of total occurrences involve primigravidas) because TPH and inoculation of the mother with fetal blood are not necessary for the development of these naturally occurring antibodies. Since the A and B antigens on the fetal and neonatal RBCs are not well developed, only a small amount of maternal antibody actually attaches to the antigen. Other body tissues and secretions also have antigen sites to which some of the circulating antibodies can adhere, thereby decreasing the potential for RBC destruction. The resulting small amounts of IgG in the plasma do not stimulate activation of the complement system; therefore, hemolysis is minimal. This lack of stimulation of the complement system and the previous factors may explain why only a small subset of the 15% of infants who are ABO incompatible with their mothers become symptomatic (Watchko, 2015).

Erythrocyte antibodies are not usually present in the circulating blood until 2 to 8 months of postnatal age, which prevents maternal inoculation with fetal anti-A or anti-B antibodies. Antibody production then increases, reaching a maximum titer at 8 to 10 years of age (Hall, 2016). The newborn becomes inoculated with A and B antigens after birth through ingestion of food and the resulting bacterial colonization. This initiates production of anti-A or anti-B antibodies that circulate in the plasma, depending on the antigens present on the RBCs.

Clinical Manifestations. The chief symptom of ABO incompatibility is jaundice within the first 24 hours of life; 90% of all affected infants are female. Blood typing and a direct Coombs test are performed (Watchko, 2015). The direct Coombs test is a measurement of the presence of antibody on the RBC surface; the indirect Coombs test is a measurement of antibody in the serum. ABO incompatibility can also be identified by the performance of an eluate test, which involves washing the RBCs of the newborn and testing the wash for anti-A or anti-B antibodies. In addition, hemolysis and anemia are minimal, although signs of a mildly compensated hemolytic state are reflected in certain CBC values. There may be an elevated reticulocyte count and the peripheral blood smear may show evidence of spherocytes, or RBCs lacking the normal central pallor and biconcave, disklike shape of the normal RBC. Because they are smaller than normal RBCs, spherocytes appear thicker. These physical characteristics result in abnormal fragility under osmotic stress. Spherocytes are not distensible or compressible because they lack the normal amount of loose cell membrane, making them more susceptible to destruction in the splenic sinusoids.

On physical examination, hepatosplenomegaly can be observed, a reflection of extramedullary erythropoiesis generated by the fetus in response to significant hemolysis. In an effort to compensate for increased cell destruction, the liver and spleen manufacture RBCs for a longer period than is usually seen in the fetus and newborn. Engorgement of the splenic sinusoids by hemolyzed RBCs contributes to splenomegaly.

Treatment. Since the antibodies involved in ABO incompatibility occur naturally, elimination of this type of incompatibility is virtually impossible. However, its effects on the fetus and newborn are much less dramatic and life threatening than those of Rh incompatibility; therefore, amniocentesis and monitoring of amniotic fluid bilirubin levels, intrauterine transfusions, and early delivery are usually not necessary. Nevertheless, problems associated with postnatal bilirubin clearance do arise, and phototherapy and possible exchange transfusion become part of the repertoire of care. These two treatment methods are discussed in further detail later in the chapter.

Rh Incompatibility

Incompatibilities involving the Rh system are the second most common alloimmune problem, but the severity of complications far surpasses that of ABO incompatibility. Antibodies never occur naturally in the Rh system; exposure to the antigen is necessary to produce antibodies. Such exposure is thought to occur through maternal inoculation with fetal RBCs by TPH or through undetectable hemorrhage during labor, abortion, ectopic pregnancy, amniocentesis, chorionic villus sampling, or percutaneous fetal procedures. **Emergency Alert: A thorough prenatal history may identify risk factors for the development of ABO or Rh incompatibility that have gone undetected.**

Spontaneous TPH occurs in 50% to 75% of all pregnancies, with the greatest and most severe occurrence at the time of delivery. Fetal RBCs can be found in 3% of all pregnancies during the first trimester, 12% in the second trimester, and 45% in the third trimester (Blackburn, 2017). Spontaneous TPH allows fetal RBCs to pass into the maternal circulation, where antibodies develop in response to any foreign RBC antigen the mother does not possess. The risk of immunization depends on the ABO status of both mother and fetus and the size of the hemorrhage. On the basis of blood type, the risk for maternal Rh immunization in an ABO-compatible Rh-negative mother and Rh-positive fetus is 16%, whereas an ABO-incompatible pregnancy with an Rh-negative mother and Rh-positive fetus runs a 1.5% to 2% risk with each pregnancy. If the volume of TPH is less than 0.1 mL RBCs, the overall risk for immunization is 3%; if the hemorrhage is greater than 5 mL, the risk increases to 50% to 65%.

The maternal Rh antibody is slow to develop and initially may consist exclusively of IgM, which cannot cross the placenta because of its molecular size. This is followed by the production of IgG, which can cross the placenta into the fetal circulation. The maximum concentration of the IgG form of antibody occurs within 2 to 4 months after termination of the first sensitizing pregnancy (Hall, 2016). If initial immunization occurs shortly before or at the time of delivery, the first Rh-positive infant born to such a mother may trigger the initial antibody response, but the infant will not be affected. However, subsequent exposure to RBCs of Rh-positive fetuses produces a rapid antibody response that consists mostly of IgG. This response results in antibody attachment to antigen sites on the fetal RBCs of these fetuses. The antibody coating of the RBCs forms the basis for a positive result on the direct Coombs test. The affected RBCs undergo agglutination, phagocytosis, and eventually extravascular hemolysis in the spleen. The by-products of hemolysis, especially bilirubin, pass through the placenta into the maternal circulation to be metabolized and conjugated by the maternal liver. The rate of destruction of fetal RBCs depends on the amount of anti-D antibodies on the cells, the effectiveness of anti-D antibodies in promoting phagocytosis, and the capability of the spleen's reticuloendothelial system to remove antibody-coated cells.

Erythroblastosis Fetalis

Hemolysis in the fetus caused by Rh incompatibility results in the disease known as erythroblastosis fetalis (EBF); the major consequences are anemia and hyperbilirubinemia. The name is derived from the presence of immature circulating RBCs (erythroblasts), which are forced into the circulation of affected fetuses to compensate for rapid destruction of fetal blood cells. The severity of the disease depends on the degree of hemolysis and the ability of

the fetus's erythropoietic system to counteract the ensuing anemia. In an attempt to compensate for rapid destruction, the fetus continues to use extramedullary organs, such as the liver and spleen, which normally would have ceased RBC production after the seventh month of gestation.

Clinical Manifestations. The clinical manifestations of EBF are similar to those of ABO incompatibility but often are more intense (see Table 13.6). Jaundice results from an exaggerated rise in bilirubin, with the premature infant exhibiting an earlier rise and a more prolonged period of elevation. Hepatosplenomegaly may be found on physical examination, along with varying degrees of hydrops. Hydrops fetalis, a late sign, is a severe, total body edema often accompanied by ascites and pleural effusions. This is only seen in approximately 25% of infants affected. Although the pathogenesis is unclear, it is thought to be the result of congestive heart failure and intrauterine hypoxia from severe anemia, portal and umbilical venous hypertension caused by hepatic hematopoiesis, and low plasma colloid osmotic pressure induced by hypoalbuminemia. Low serum albumin levels are a consequence of altered hepatic synthesis, which may be due to local cellular necrosis and compromised intrahepatic circulation.

TABLE 13.6

CONTRAST BETWEEN RH AND ABO INCOMPATIBILITY

	Rh Incompatibility	ABO Incompatibility
Rh-negative mom	Yes	No
First pregnancy affected	Rarely	Often
Cord bilirubin elevated	Yes	Sometimes
Early anemia prominent	Yes	No
Jaundice in first 24 hours	Yes	Yes
Hepatosplenomegaly	Yes	Sometimes
Nucleated red blood cells	Very common	Quite common
Spherocytes	No	Yes
Reticulocytosis	Yes	Yes
Maternal antibodies	Yes	Not always
Direct Coombs test	Positive	Positive or negative
Indirect Coombs test	Negative	Positive

Source: Modified from Ohls, R. (2015). Anemia. In R. Polin & M. Yoder (Eds.), *Workbook in practical neonatology* (5th ed., pp. 107–136). Philadelphia, PA: Elsevier.

All these factors can lead to portal and venous hypertension and edema. The severity of the anemia and hypoalbuminemia affects the degree of extravasation of fluid into the tissue.

Altered hepatic synthesis can impair production of vitamin K and vitamin K–dependent clotting factors, which can lead to hemorrhage in these infants. Petechiae and prolonged bleeding from cord and blood sampling sites may be initial signs of clotting abnormalities. Transient hypoglycemia that occurs secondary to hyperplasia of the pancreatic islet cells is also associated with moderate to severe EBF. Products of RBC hemolysis are thought to inactivate circulating insulin, promoting increased insulin release and subsequent pancreatic beta-cell hyperplasia. Another theory suggests that potassium or amino acids released from hemolyzed cells may directly stimulate insulin production or indirectly produce this effect by increasing glucagon secretion. Approximately one third of surviving erythroblastotic infants have low blood glucose levels and elevated plasma insulin levels.

Antenatal Therapy. Adequate antenatal care is important in safeguarding the fetus that may be affected by EBF. Proper screening of any pregnant woman at her first prenatal visit is essential and should include blood type and Rh factor. If the mother is Rh negative, the father's blood type should also be ascertained. If the father is Rh positive, it is essential to determine Rh immunization of the mother by Coombs testing, specifically the indirect Coombs test. In addition to blood typing, a concise obstetrical history regarding any previous spontaneous or therapeutic abortions or delivery of an affected infant is important to ensure appropriate management of the current pregnancy.

Women who are sensitized require more surveillance throughout the pregnancy than their unsensitized counterparts, and women who have previously given birth to affected infants require the greatest degree of care. Serial maternal anti-D antibodies are monitored. If the titers reach a critical threshold (≥1:16) then the fetus is monitored closely for the development of fetal anemia. Monitoring includes Doppler studies of the middle cerebral artery and fetal imaging for signs of an enlarged placenta, hepatomegaly, and hydrops fetalis (Castro & Hobel, 2016). Evidence of fetal anemia will result in percutaneous umbilical blood sampling to assess fetal hemoglobin and Hct. Further management can include intrauterine or intraperitoneal transfusions, steroids to promote fetal lung maturity, monitoring of fetal well-being and growth, and assessing the need for an early delivery (Castro & Hobel, 2016).

Unsensitized Rh-negative mothers can benefit from antenatal and postpartum administration of RhIgG. Prophylactic RhIgG should be administered to all unsensitized Rh-negative mothers at 28 weeks' gestation. Mothers should receive a second dose of RhIgG within 72 hours following delivery if it is determined that the infant is Rh positive. The approach to RhIgG is based on the documented presence of fetal RBCs. The erythrocyte rosette screen detects the presence of fetal whole blood in the maternal circulation. A Kleihauer–Betke test should be performed following a positive rosette screen to determine the percentage of fetal RBCs present (ACOG Committee on Practice Bulletins—Obstetrics, 2017). With the use of RhIgG after delivery, the incidence of Rh immunization was dramatically reduced to 1% to 1.8%. Because sensitization was known to occur without evidence of TPH at the time of delivery, the question was raised whether antenatal sensitization occurred in response to frequent, small, and undetectable hemorrhage before or during labor. For this reason, antenatal administration of RhIgG was initiated to eliminate such cases of alloimmunization. Antenatal administration has further reduced the incidence to as low as 0.2% (ACOG Committee on Practice Bulletins—Obstetrics, 2017). However, sensitization during pregnancy may still occur in Rh-negative mothers. Reasons for this

can include ineffective dose of RhIgG or failure to provide RhIgG within 72 hours of a sensitizing event during pregnancy, failure to administer a prophylactic dose of RhIgG during the third trimester, or unrecognized, spontaneous TPH (Fyfe et al., 2014).

The manner in which RhIgG works to prevent sensitization of the D antigen is not fully understood. Two known effects of the anti-D antibody are that it prevents antigen-induced B lymphocyte antibody production in the mother, and it adheres to the D-antigen sites on the RBCs in the fetus that could cross the placenta and enter the maternal circulation, which then interferes with the immune response to the D antigen. Agglutination, hemolysis, and removal of these foreign RBCs occur before the maternal immune system can recognize the invasion and develop antibodies that would transplacentally cross into the fetus (Hall, 2016).

Potential obstetrical conditions occurring during the first or second trimester, which may require RhIgG prophylaxis because they can increase the risk of sensitization by increasing the chances of TPH, are as follows:

- Therapeutic or spontaneous abortion of any type; the incidence of TPH is higher with therapeutic abortion (three in 30 women may be sensitized)
- Any procedure that could cause TPH such as an amniocentesis, chorionic villus sampling, or percutaneous umbilical sampling (risk is low when performed by an experienced professional [Meleti et al., 2013])
- Ectopic pregnancies or hydatidiform moles
- Abdominal trauma
- Antepartum bleeding, as with placental abruption or placenta previa

Failure to administer RhIgG after such occurrences may leave these women at risk for sensitization. The ACOG (Committee on Practice Bulletins—Obstetrics, 2017) recommends a dose of 50 mcg for high-risk situations that arise before 12 weeks' gestation and 300 mcg after 12 weeks' gestation, with the 300-mcg dose repeated at 28 weeks' gestation. RhIgG has a half-life of 23 to 26 days and is effective for approximately 2 weeks after antigen exposure. It is essential to maintain an adequate level of anti-D antibodies throughout pregnancy to maintain protection, so if it is given prior to 28 weeks' gestation, it is advised to repeat it every 12 weeks until delivery (Mintz, 2010).

The timing of the dose after delivery is important; administration within 72 hours of delivery is recommended. The dose after delivery allows a maximum estimated fetal transfusion of 30 mL of whole blood or 15 mL of packed RBCs, which leaves 1% of postpartum mothers without full coverage. If massive TPH is suspected, the dose of RhIgG may need to be increased to provide adequate amounts of anti-D antibodies. After administration of RhIgG, the Kleihauer–Betke test can be performed on the mother's blood to check for RBCs with fetal hemoglobin and to help determine the need for additional RhIgG.

By reducing the incidence of EBF, there was at one time a fear of having a reduced supply of RhIgG, as there would be a reduced number of available immunized donors. While there are still women who have had their children and ask to be sensitized to help others, the majority of donors now are male who have been DNA typed to the RBCs that are used to sensitize them. DNA typing prevents the donors from developing anti-C, Kell, and other antibodies. A monoclonal antibody was developed, but it did not have the same success rates as the polyclonal antibodies in the market.

Treatment. On delivery of an infant with EBF, assessment of the newborn's cardiorespiratory status is of utmost importance. Because of ascites, pleural effusions, and circulatory collapse, these infants often require stabilization of the airway by intubation and mechanical ventilation. If peritoneal or pleural fluid prevents adequate chest excursion, paracentesis may be required to remove fluid from the abdominal cavity, or thoracentesis may be needed to drain excess pleural fluid.

Delivery of an infant shortly after intraperitoneal transfusion may not allow adequate time for absorption of blood from the peritoneal cavity because the rate of absorption is variable, especially if the infant is hydropic (Castro & Hobel, 2016). The unabsorbed portion could lead to diminished lung expansion, resulting in respiratory failure or restricted mechanical ventilation. Such infants may require paracentesis for removal of blood from the peritoneal cavity.

After initiation of respiratory support, the infant should be assessed for adequacy of circulating blood volume. If the infant is severely hydropic, the inevitable anemia must be corrected with transfusions of packed RBCs, since an exchange transfusion may not be tolerated until the intravascular RBC volume is replenished. Transfusion is accomplished with O-negative or type-specific Rh-negative blood cross-matched against maternal blood. Initial use of a single-volume or partial exchange may offer a degree of cardiovascular stability before a double-volume exchange is attempted. Congestive heart failure, not present at the time of intravascular volume depletion, may become apparent as the infant is transfused. At times, a severely affected infant, while often normovolemic, may benefit from inotropic support and diuretic therapy to improve cardiac output.

Prenatal damage to the liver can adversely affect the production of coagulation factors in such infants, making them prone to bleeding disorders. Hepatic damage can intensify any hyperbilirubinemia present, because the hepatic substances required for conjugation may also be impaired. Laboratory evaluation of the infant affected by EBF should consist of liver function studies, Hct determinations, and evaluation of coagulation status.

Nursing care of the infant affected by EBF involves scrupulous attention to the infant's cardiorespiratory status and vital signs. The infant needs to be positioned so as to reduce abdominal pressure on the diaphragm which will permit better chest expansion. Maintaining a normal Pao_2 and avoiding overventilation may prevent barotrauma to lungs already compromised by pleural effusions. The lungs may be hypoplastic if their growth has been sufficiently compromised by hydrops in-utero, making ventilation difficult and predisposing the infant to extraventilatory air. Vital signs are usually assessed every hour until the infant's condition has stabilized. Hct and bilirubin levels should be checked frequently during the first few hours and days of life to maintain adequate circulating blood volumes and to prevent toxic levels of bilirubin by timely initiation of therapy. If the cord bilirubin levels are significantly elevated, exchange transfusion may be necessary shortly after birth. A newer therapy that has been proven to be safe and effective is the administration of intravenous immunoglobulin (IVIG) to the neonate with hemolytic disease that has a rapidly rising serum bilirubin level despite intense phototherapy (Maisels et al., 2004). **Emergency Alert: Bilirubin neurotoxicity and, ultimately, kernicterus remain a serious complication of hyperbilirubinemia. It is critical that neonatal nurses remain hypervigilant in their assessment of an infant with elevated bilirubin, especially when the total serum bilirubin (TSB) is greater than 20 mg/dL.**

If bilirubin levels do not require immediate exchange, blood levels should be checked every 4 to 8 hours, depending on the initial cord-blood levels and subsequent rate of rise. In Rh incompatibility, exchange is imminent if the rate of rise exceeds 1 mg/hour for the first 6 hours of life. The interval of blood sampling for bilirubin may be increased to 6 to 12 hours after the first 48 hours of life.

The major therapies used to control excessive unconjugated bilirubin levels are similar for all problems resulting in elevated unconjugated bilirubin levels. Phototherapy and exchange transfusion, the most frequently used therapies, are discussed later in the chapter.

Analysis of Laboratory Data. The following laboratory data can be helpful in the diagnosis and treatment of EBF.

- The mother's and infant's blood and Rh types
- Coombs reactivity: The infant's RBCs are coated with anti-D antibodies, resulting in a positive direct Coombs test result; on occasion, the heavy coating of neonatal RBCs with antibody can lead to a false Rh typing (Rh negative); if the direct Coombs test result is positive, the infant should be considered Rh positive.
- The infant's Hct, reticulocyte count, and RBC morphologic characteristics: The presence of immature cells or spherocytes helps distinguish Rh incompatibility from ABO incompatibility.
- Plasma bilirubin levels: The initial cord-blood bilirubin level and the rate of rise determine the appropriate timing of any exchange transfusion needed to control bilirubin levels. Cord bilirubin levels are closely associated with the severity of the disease and the mortality rate.

BILIRUBIN METABOLISM AND HYPERBILIRUBINEMIA

Bilirubin production begins as early as 12 weeks' gestation. It is the primary degradation product of hemoglobin, although 20% to 30% is derived from nonerythroid sources such as tissue heme. Bilirubin is produced after completion of the natural life span of the RBC, but ineffective erythropoiesis or premature destruction of blood cells can increase its production. In RBC destruction, the aging or hemolyzed RBC membrane ruptures, releasing hemoglobin that is phagocytized by macrophages. The hemoglobin molecule then splits into a heme portion and a globin portion. Bilirubin is derived from the degradation of the heme ring in the heme portion that is catalyzed by heme oxygenase. The ferric heme breaks down to the ferrous form and then is cleaved to form carbon monoxide and biliverdin. Biliverdin is further reduced by the enzyme biliverdin reductase to form bilirubin, and carbon monoxide joins with heme to form carboxyhemoglobin.

The four forms of circulating bilirubin are (1) conjugated (water-soluble) bilirubin (which is excretable through the kidneys and intestines), (2) conjugated covalently bound bilirubin (which is attached to serum albumin and not found in neonates younger than 2 weeks of age), (3) unconjugated (insoluble in water) bilirubin (which is reversibly bound to albumin), and (4) free bilirubin (which is unconjugated and unbound). The measurement of conjugated (direct) bilirubin identifies the amount of bilirubin that reacts directly with van den Bergh's reagent. The portion of bilirubin reversibly bound to albumin is lipid soluble. It does not react with van den Bergh's reagent until it is combined with alcohol, hence the term *unconjugated (indirect) bilirubin*. Free bilirubin is not attached to albumin and can easily cross the blood–brain barrier, causing the damage seen in kernicterus. Measurements of conjugated and unconjugated bilirubin are important in the evaluation of the hyperbilirubinemic infant and provide valuable information for the diagnosis and method of treatment (Downs & Gourley, 2015).

Although bilirubin is found in stool and amniotic fluid, the major route of elimination in the fetus is through the placenta. For this reason, bilirubin must be retained in the unconjugated form to allow its passage into the maternal circulation. Consequently, the enzyme systems found in the fetus enhance the retention of bilirubin in the unconjugated form. Persistence of some of these fetal mechanisms during the newborn period can contribute to jaundice. Plasma concentrations of bilirubin are usually low in the fetus, except in cases of severe hemolytic disease. All bilirubin in the cord blood of the fetus is the unconjugated variety, which is effectively metabolized, conjugated, and excreted by the maternal liver and gallbladder. The mean cord-blood bilirubin concentration in an infant unaffected by hemolytic disease is 1.8 mg/dL, regardless of the infant's gestational age or weight.

In the newborn, the major routes of bilirubin excretion are through the intestine and the kidneys. As the production of bilirubin exceeds the newborn liver's capacity to conjugate and eliminate it, plasma levels begin to rise rapidly. Jaundice becomes noticeable when the serum concentration reaches three times the amount normally present in the serum. The conjunctivae become visibly jaundiced at serum levels exceeding 2.5 mg/dL. In the full-term infant, jaundice usually becomes apparent within 2 to 4 days after birth and lasts until the sixth day, reaching a peak concentration of 6 to 7 mg/dL. Although infants born at 37 weeks' gestation or later are considered term, they are more likely to reach or exceed serum bilirubin levels of 13 mg/dL or higher than are infants born at 40 weeks' gestation. The preterm infant has cord-blood bilirubin levels similar to those of the term infant, but peak levels are higher, jaundice lasts longer, and levels peak later, at 5 to 7 days. Among preterm infants, 63% reach levels of 10 to 19 mg/dL, and 22% reach levels above 15 mg/dL.

Although the neonatal liver's conjugating mechanisms are reduced during the first few days of life, the liver is able to metabolize and excrete two thirds to three quarters of the bilirubin circulating throughout the body. Initially, bilirubin is transported in the plasma, bound to albumin at two sites—a primary binding site that has a strong bond and a secondary site that has a weak bond. When available albumin binding sites are saturated, bilirubin circulates freely in the plasma. It is this portion of unconjugated bilirubin that can migrate into brain cells, causing damage known as kernicterus. The occurrence of kernicterus is related to the amount of diffusible, loosely bound bilirubin, and the availability of albumin binding sites (Downs & Gourley, 2015).

When bilirubin reaches the liver, it is transferred from plasma albumin, across the cell membrane of the liver, and into the liver cell. Two proteins, Y and Z, also called ligands, affect bilirubin transfer from plasma to the liver. Here the bilirubin is either stored in the cell cytoplasm or removed from the ligands and conjugated in the hepatic endoplasmic reticulum. Conjugation is essential for the excretion of bilirubin into bile. Eighty percent of bilirubin is conjugated with glucuronic acid, becoming bilirubin glucuronide. Glucuronosyltransferase is the important hepatic enzyme required for the production of bilirubin glucuronide. Ninety-five percent of bilirubin glucuronide is excreted into bile and subsequently into the intestine.

Effective excretion of bilirubin from the intestine depends on the length of time needed for the passage of stool and on the presence of substances that break down conjugated bilirubin. The newborn may have diminished bowel motility and delayed meconium passage, which allow longer exposure of stool to bilirubin glucuronidase, the enzyme responsible for breaking down conjugated bilirubin. The action of this enzyme, in conjunction with the newborn's lack of the intestinal flora required to reduce bilirubin to urobilinogen, converts the conjugated form to the unconjugated form, which is then reabsorbed by the intestine and enters the enterohepatic circulation where it returns to the liver for conjugation (Downs & Gourley, 2015).

Kernicterus

Kernicterus is a chronic and preventable form of acute bilirubin encephalopathy. The exact incidence of kernicterus is unknown. It is estimated to occur in 0.4 to 2.7 cases per 100,000 live births (Watchko & Tiribelli, 2013). There are conflicting reports as to whether there is a resurgence in the occurrence of kernicterus (Kaplan, Bromiker, & Hammerman, 2011). Kernicterus continues to occur and remains a serious complication of hyperbilirubinemia. Potential causes include a lack of systematic bilirubin screening and adherence to recommended guidelines especially for early discharges, home births and births at a non-hospital birthing center, breastfeeding, unrecognized hemolysis, and genetic influences (Christensen et al., 2012). The guidelines from the AAP Provisional Committee for Quality Improvement & Subcommittee on Hyperbilirubinemia (Maisels et al., 2004), updated in 2009 (Maisels et al., 2009), clearly state that newborn infants should have their bilirubin levels screened and assessment of risk factors done prior to hospital discharge and again within 48 to 72 hours after discharge. Systematic screening guidelines have been found to significantly decrease the incidence of kernicterus (Christensen et al., 2012).

Kernicterus occurs when the albumin binding sites are filled, allowing increased amounts of free bilirubin to pass into the central nervous system (CNS). Free bilirubin easily crosses the blood–brain barrier and is transferred into the brain cells, causing obvious yellow staining of the brain tissue (kernicterus) that is similar to the effect on the skin. The areas of the brain usually affected by the staining are the basal ganglia, hippocampus, dentate nucleus, substantia nigra, cerebellum, and nuclei of the floor of the fourth ventricle (Downs & Gourley, 2015). Kernicterus is associated with varying degrees of neurologic damage, but a direct correlation cannot be drawn between serum total bilirubin levels and the severity of involvement. While numerous risk factors play a role, the risk for kernicterus increases as serum total bilirubin rises above 20 mg/dL, with the highest risk associated with serum levels above 30 mg/dL. The development of kernicterus and the subsequent neurologic sequelae may be a reflection of the imbalance among rate of bilirubin production, binding, conjugation, and elimination (Kaplan, Wong, Sibley, & Stevenson, 2015; Shapiro, 2012). The available evidence suggests that measuring unbound bilirubin, bilirubin–albumin binding capacity, and bilirubin–albumin ratios, rather than serum total bilirubin concentrations, are better correlated with the appearance of subsequent CNS abnormalities. However, prospective studies are needed to include these measures as a part of standard clinical practice (Hulzebos & Dijk, 2014; Kaplan et al., 2015; Morioka, Iwatani, Koda, Iijima, & Nakamura, 2015).

Many factors can influence bilirubin binding to albumin and increase the risk of kernicterus at lower bilirubin levels, including the following:

- The total amount of available serum albumin: Premature infants normally experience a relative hypoproteinemia and have fewer albumin binding sites available for free bilirubin.
- The presence of other substances competing for available binding sites: Certain drugs (e.g., sulfonamides, cephalosporins, penicillins, salicylates, sodium benzoate) compete with bilirubin for binding sites or displace bilirubin loosely attached to binding sites. Of note, ibuprofen was found to displace bilirubin, raising unbound levels during in-vitro studies. However, ibuprofen was not found to increase unbound bilirubin levels during in-vivo studies (Morioka et al., 2015).
- Acidosis and hypoxia: Increased production of hydrogen ions and implementation of anaerobic metabolism can impede bilirubin binding. Albumin's ability to bind bilirubin drops to half its potential at a serum pH of 7.1, with free fatty acids produced during anaerobic metabolism competing for albumin binding sites. The simultaneous presence of acidosis and hypoxia, which can open the blood–brain barrier, can expose a sick infant to the development of kernicterus at much lower serum bilirubin levels.

Clinical Manifestations. Kernicterus initially presents during the first few days of life as acute bilirubin encephalopathy. Signs of acute encephalopathy include lethargy or irritability and poor eating. As the encephalopathy progresses, alterations in muscle tone may manifest as hypertonia and hypotonia, a high-pitched cry develops, and further signs include paralysis of upward gaze, opisthotonic posturing, and spasticity. In its chronic and irreversible form, permanent signs of kernicterus include auditory processing disturbance with or without deafness, continued paralysis of upward gaze, choreoathetoid cerebral palsy, and tooth enamel abnormalities (Kaplan et al., 2011). Preventing elevated levels of free bilirubin is the primary means of eliminating kernicterus. Prevention may require phototherapy for slowly rising levels but almost certainly demands exchange transfusion if the rise is rapid and marked.

Nonimmune Causes of Hyperbilirubinemia

The presence of jaundice during the first 24 hours of life or bilirubin levels that are excessive based on the infant's age are not considered physiologic and require further investigation (Kaplan et al., 2015). Many conditions other than blood group incompatibilities can cause jaundice in the newborn. Most of the commonly seen disorders result in elevated levels of unconjugated rather than conjugated bilirubin. These pathologic conditions can be classified as (a) those that cause increased breakdown of RBCs (e.g., sepsis, drug reactions, and extravascular blood); (b) those that interfere with bilirubin conjugation (e.g., breast milk jaundice, drug interactions, hypothyroidism, acidosis, and hypoxia); and (c) those that cause abnormal bilirubin excretion (e.g., hypoxia or asphyxia, bowel obstruction, ileus, and congestive heart failure). The single factor most implicated in hyperbilirubinemia is prematurity, with the severity of jaundice directly correlated to declining gestational age. The premature infant is thought to be subject to a combination of increased RBC breakdown secondary to reduced RBC life span and impaired bilirubin conjugation as a result of liver immaturity (Blackburn, 2017).

Increased Red Blood Cell Breakdown

Several problems that arise in the perinatal period are associated with excessive and premature destruction of the RBCs by hemolysis. Neonatal bacterial and viral infections and intrauterine viral infections, especially those of the TORCH complex (toxoplasmosis, other agents, rubella, CMV, and herpes simplex), have been implicated in the hemolytic destruction of RBCs. Certain medications, such as the synthetic analogues of vitamin K or large doses of natural vitamin K, also induce RBC destruction. Other conditions prevalent in the premature and term newborn can result in the extravasation of large amounts of blood (e.g., cephalohematoma and pulmonary or intracerebral hemorrhages). These extravascular collections of blood cells must undergo hemolysis to be reabsorbed by the body. Significant hemolysis, regardless of the cause, increases the bilirubin load on a metabolically immature neonatal liver. This increased load often results in hyperbilirubinemia in the newborn.

Interference With Bilirubin Conjugation

Breast Milk Jaundice. Breast milk jaundice affects a small percentage of all breastfed babies and can be divided into two types, breastfeeding jaundice and breast milk jaundice, each with a different time of onset and a different underlying cause. However, overlap may occur between the two types. In breastfeeding jaundice, the infant is affected within the first few days of life. The etiology of this condition is not fully understood, but is thought to be due to a combination of maternal and infant factors that lead to diminished fluid intake and dehydration in the infant. Predisposing maternal factors include limited maternal milk supply, engorgement, cracked nipples, poor feeding technique, and maternal illness or fatigue. Neonatal factors include poor suck, illness, lethargy that accompanies hyperbilirubinemia, and dehydration. Poor intake leads to poor stool output and increased enterohepatic resorption of unconjugated bilirubin. The recommended treatment is phototherapy and alleviation of dehydration. Frequent breastfeeding with avoidance of supplementation, lactation counseling, and monitoring of weight gain and stool output are advised.

a. Breast milk jaundice is a separate entity that is attributed to a change in the chemical or physical composition of breast milk; it usually occurs after the first 4 to 7 days of life (Deshpande & Wagle, 2017). Bilirubin levels can reach 12 to 20 mg/dL between 8 and 15 days and may remain elevated for as long as 3 months. The infant appears healthy with normal weight gain and stool output, and no evidence of RBC hemolysis is seen. However, it is recommended that bilirubin levels greater than 12 mg/dL or persistent into the third week of life may warrant further investigation (Flaherman et al., 2017; Preer & Philipp, 2011). Breast milk jaundice is not well understood, but the following factors, as summarized by Deshpande and Wagle (2017), are believed to play a role: (a) Two substances found in breast milk, pregnanediol and nonesterified fatty acids, interfere with bilirubin conjugation or increase enterohepatic circulation, resulting in resorption of bilirubin from the intestine. They are thought to inhibit glucuronyl transferase, the enzyme necessary for bilirubin conjugation in the liver. However, the role of these two substances in the interference with glucuronyl transferase activity remains questionable. (b) An increase in enterohepatic bilirubin due to increase of beta-glucuronidase activity in breast milk and subsequently the intestines of breastfed infants as well as the delayed establishment of enteric flora. (c) A defect in the UGT gene *UGT1A1*, which is responsible for conjugation and elimination of bilirubin. (d) Mutation of the solute carrier organic anion transporter protein SLCO1B1, which results in reduced hepatic uptake of unconjugated bilirubin. (e) Presence of inflammatory cytokines in human milk, in particular IL-1-beta and IL-6. Both of these are known to be cholestatic and reduce uptake, metabolism, and excretion of bilirubin. (f) High levels of epidermal growth factor (EGF) in breast milk and the serum have been found in neonates with breast milk jaundice. It is thought that the increased EGF enhances bilirubin absorption and uptake, contributing to the presence of jaundice, as well as (g) serum alpha-fetoprotein levels are higher in these infants, but the significance of this is yet to be determined (Deshpande & Wagle, 2017).
b. When breastfeeding is discontinued, the bilirubin level falls within 24 to 48 hours, dropping to half its previous peak level by 48 hours. With resumption of breastfeeding, the bilirubin level starts to rise but at a much slower pace. Interruption of breastfeeding is not recommended; instead, continued and frequent breastfeeding is encouraged. However, the healthcare provider has the option to supplement nursing with formula or to interrupt breastfeeding and substitute formula, depending on the degree of bilirubin elevation. Supplementation of nursing with water or glucose water does not appear to have any effect on bilirubin levels in healthy term infants.

Drugs That Interfere With Bilirubin Conjugation. Certain medications ingested by the mother and passed transplacentally to the fetus (e.g., salicylates, sulfa preparations) can interfere with the ability of albumin to bind bilirubin. Administration of these drugs to the newborn can produce the same effect. Other medications, such as sodium benzoate, a commonly used preservative, compete with bilirubin for albumin binding sites.

Hypothyroidism. Hypothyroidism is one of the more common metabolic disorders associated with hyperbilirubinemia. Of all infants with hypothyroidism, 10% have elevated bilirubin levels lasting several weeks to months. The suspected mechanism for jaundice is theorized to be a delay in glucuronosyltransferase synthesis or impairment of hepatic proteins that bind bilirubin and remove it from the plasma. The plasma membrane of liver cells may also be altered, resulting in decreased bilirubin influx into the hepatic cells (Kaplan et al., 2015).

Acidosis and Hypoxia. As previously stated in the discussion of kernicterus, a drop in serum pH alters albumin's ability to bind bilirubin. The accompanying increase in the production of free fatty acids promotes competition between fatty acids and bilirubin for binding sites.

Abnormal Bilirubin Excretion. Any disease state resulting in abnormal bilirubin excretion can raise serum bilirubin levels significantly. This is seen in hepatic dysfunction secondary to such entities as hypoxia or asphyxia, bowel obstruction, ileus, and congestive heart failure. However, these conditions have a tendency to elevate both the conjugated and unconjugated bilirubin levels. The diminished bowel motility associated with these conditions lengthens the time during which beta-glucuronidase, which is naturally present in the gut, can act on conjugated bilirubin in the stool. This enzymatic reaction converts conjugated bilirubin into the unconjugated form, which is reabsorbed into the intravascular compartment through the enterohepatic circulation. Direct hepatocellular damage associated with cholestasis and bacterial and viral infections can further impair the liver's ability to conjugate bilirubin (Kaplan et al., 2015).

Treatment of Hyperbilirubinemia

Phototherapy. Phototherapy reduces unconjugated bilirubin through photooxidation and photoisomerization, which changes bilirubin into water-soluble forms that can bypass the need for conjugation in the liver and be readily excreted in bile and urine (Maisels, 2015). Photooxidation involves the oxidation of bilirubin pigment deposited in the skin and its conversion into colorless products that can be excreted into the urine. Of the total body bilirubin concentration, 15% can undergo photodegradation through oxidation. Photoisomerization involves the conversion of bilirubin polymers present in the skin into excretable isomers. When the natural form of bilirubin is exposed to blue light at certain wavelengths, it undergoes photoisomerization. This changes it from a tetrapyrrole, a lipid-soluble substance, into five water-soluble isomers. Four of these isomers are excreted into bile without undergoing conjugation. Two are unstable isomers that are incorporated into bile and

must be promptly eliminated from the gastrointestinal tract as a component of stool or they revert to their natural forms, resulting in resorption of bilirubin from the gut and recirculation into the plasma. Two other isomers remain relatively stable and account for most of the bilirubin found in bile. The fifth isomer, lumirubin, is a stable, water-soluble form of bilirubin that is eliminated more rapidly through urine and bile (Bhutani & Lamola, 2017). Its conversion is the rate-limiting step in the conversion of bilirubin for elimination by phototherapy and, thus, plays a critical role in the decrease in bilirubin levels associated with phototherapy (Kaplan et al., 2015).

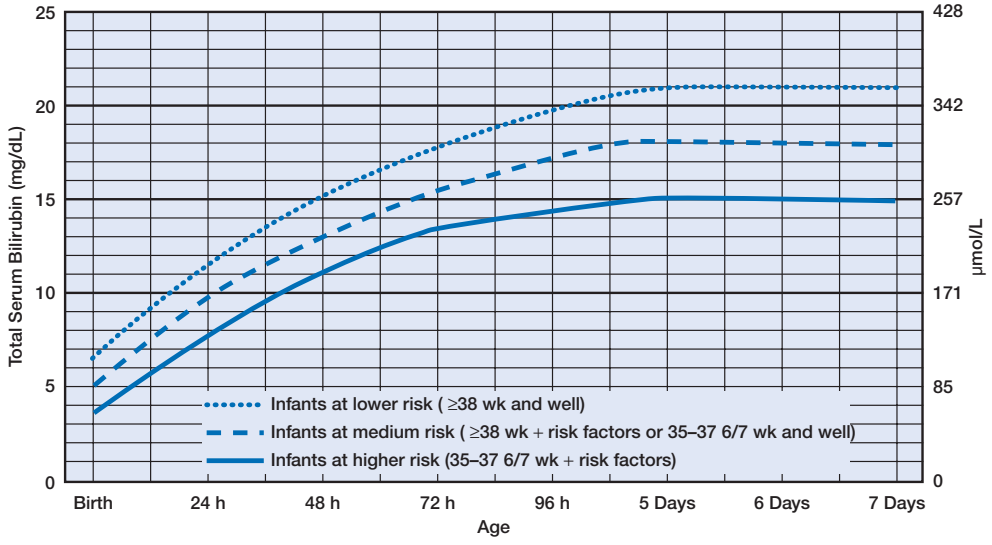
Phototherapy, alone, is not adequate therapy for a rapidly rising bilirubin level, but it is effective in treating moderate hyperbilirubinemia that has not reached or exceeded levels known to be associated with kernicterus and in reducing the need for exchange transfusions after the first 12 hours of life. The effectiveness of phototherapy is influenced by spectral qualities of the light, intensity of the light or spectral irradiance, distance between the light and the infant's skin, body surface area exposed to the light, cause of jaundice, and TSB when phototherapy is initiated (Maisels et al., 2004). Intensive phototherapy can produce a decline of 2 mg/dL of TSB within 4 to 6 hours (Bhutani et al., 2011) and can produce a reduction in the initial TSB by 30% to 40% within the first 24 hours of treatment (AAP Subcomittee on Hyperbilirubinemia, 2004). This is a reflection of the length of exposure necessary for phototherapy to exhibit its effectiveness. The AAP Provisional Committee for Quality Improvement & Subcommittee on Hyperbilirubinemia (Maisels et al., 2004) revised a set of guidelines for the initiation of phototherapy (Figure 13.6) and exchange transfusion (Figure 13.7) in infants greater than or equal to 35 weeks' gestation. Suggested TSB levels for initiation of phototherapy and exchange transfusion for the preterm infant based on gestational age are found in Figure 13.8.

Recommended levels for the use of phototherapy or exchange transfusion must be adjusted downward for prematurity, acidosis, hypoxia, respiratory distress, asphyxia, and neurologic decompensation (Figure 13.7). Diminished bilirubin-binding capacity of albumin and decreased amounts of circulating albumin expose these infants to increased amounts of free bilirubin, which can easily cross the blood–brain barrier and increase the susceptibility of the infant to bilirubin toxicity.

Although no significant adverse effects are attributed to the use of phototherapy, it is not without associated side effects. Some of these problems include dermal rash, lethargy, abdominal distention, possible eye damage, dehydration caused by increased insensible water loss through the skin and digestive tract, thrombocytopenia, hypocalcemia, and secretory diarrhea possibly as a result of a temporary intestinal lactose deficiency. Another effect of phototherapy seen in infants with a significant direct bilirubin component is "bronze baby" syndrome. This syndrome is thought to be due to skin deposition or a photoproduct of bilirubin decomposition, possibly copper porphyrins, which causes bronzing of the skin and urine. Although no harmful effects can be attributed to the bronzing, it can last for several weeks to several months and is somewhat alarming to parents (Kaplan et al., 2015).

The administration of albumin to an infant undergoing phototherapy may reduce the amount of bilirubin available in the skin for photoisomerization. In an attempt to saturate the increased available albumin binding sites, free bilirubin is drawn into the vascular compartment from the skin, where phototherapy exerts its effect. For this reason, use of albumin in the infant undergoing phototherapy should be carefully weighed.

Collaborative Management. Infants who require phototherapy benefit most from light in the blue-green spectrum in the wavelength range at which photoisomerization occurs most efficiently: that is,



- Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.
- Risk factors = isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis, or albumin <3.0 g/dL (if measured).
- For well infants 35-37 6/7 weeks can adjust TSB levels for intervention around the medium risk line. It is an option to intervene at lower TSB levels for infants closer to 35 weeks and at higher TSB levels for those closer to 37 6/7 weeks.
- It is an option to provide conventional phototherapy in hospital or at home at TSB levels 2-3 mg/dL (35-50 mmol/L) below those shown, but home phototherapy should not be used in any infant with risk factors.

FIGURE 13.6 Guidelines for phototherapy in hospitalized infants of 35 or more weeks' gestation.

G6PD, glucose-6-phosphate dehydrogenase; TSB, total serum bilirubin.

Source: From Maisels, M. J., Baltz, R. D., Bhutani, V. K., Newman, T. B., Palmer, H., Rosenfeld, W., . . . Weinblatt, H. B. (2004). Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics, 114*, 297–316. doi:10.1542/peds.114.1.297. Copyright © 2004 American Academy of Pediatrics.

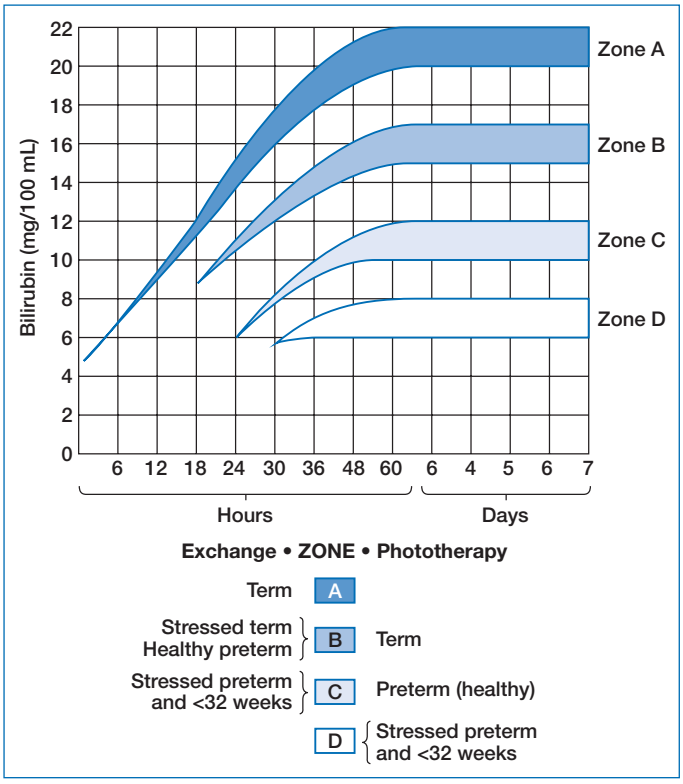


FIGURE 13.7 The rate of increase in bilirubin levels, gestational age, and the newborn's general condition determine the type of treatment for hyperbilirubinemia and the rapidity of its initiation. This chart is a useful guideline for initiating phototherapy or exchange transfusion in hyperbilirubinemic infants.

Source: From Pernoll, M., et al. (1986). Neonatal hyperbilirubinemia and prevention of kernicterus. In M. Pernoll, G. I. Benda, S. G. Babson, & K. Simpson (Ed.), *Diagnosis and management of the fetus and neonate at risk* (5th ed.). St. Louis, MO: Mosby.

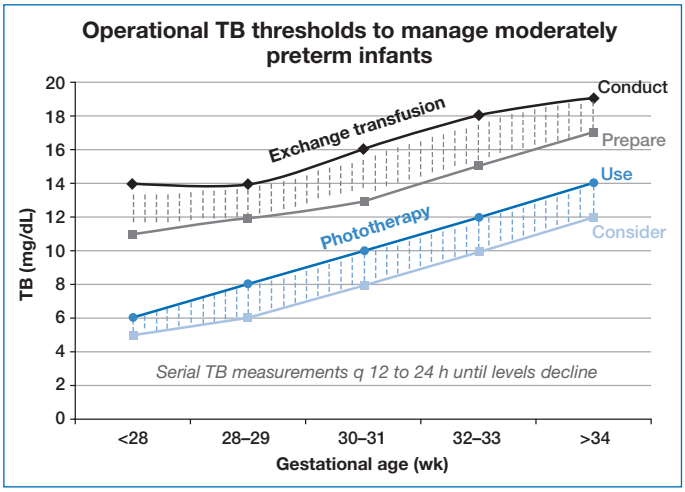


FIGURE 13.8 Suggested thresholds for phototherapy and exchange transfusion in preterm infants less than 35 weeks' gestation.

Source: From Bhutani, V. K., Wong, R. J., & Stevenson, D. K. (2016). Hyperbilirubinemia in preterm neonates. *Journal of Perinatology, 43*(2), 215–232. doi:10.1016/j.clp.2016.01.001

425 to 550 nm. In addition to the appropriate wavelength, effective illumination must be maintained. Spectroradiometric readings of at least 8 to 10 μW/cm^2/nm are required to produce the isomer lumirubin. Intensive phototherapy requires an irradiance of greater than 30 μW/cm^2/nm (Blackburn, 2017). For optimum therapy, phototherapy units should be checked for adequacy of light levels by nursing or bioengineering staff. Prolonged exposure to phototherapy lights may cause retinal damage, which can be minimized with adequate eye protection. Phototherapy units and eye protection should be removed for short periods throughout the day to provide the infant with visual stimulation and interaction with parents and caregivers. Nurses should also be aware that they may experience headaches from prolonged exposure to phototherapy lights.

Infants undergoing phototherapy require temperature stabilization appropriate for their size and overall condition. A larger infant who is basically well can be nursed in an open crib, but the sick term, premature, or low-birth-weight (LBW) infant requires temperature control through the use of open warmers or closed incubators. Adequate fluid intake and compensatory fluid adjustments for increased insensible water and stool loss may be required to prevent dehydration in these infants. While the infant is receiving phototherapy, bilirubin levels must be monitored frequently to assess the effectiveness of therapy and the need for exchange transfusion. Because phototherapy lights can alter blood bilirubin results, the lights should be turned off when drawing blood for serum bilirubin determinations.

Many hyperbilirubinemic infants, who are healthy and not in need of thermoregulation or exchange transfusion, can be cared for at home as long as the AAP guidelines are met. The parents of these infants must have access to home phototherapy equipment and a medical supply company to service the equipment, as well as the support of their medical caregiver. If the infant can remain normothermic in an open crib without clothing, home phototherapy may be considered a cost-effective alternative to hospitalization. The same precautions regarding protective eye covering and adequate fluid intake must be observed in these infants. Frequent determination of bilirubin levels is required to ensure adequate treatment, and blood may be drawn daily for this purpose at the physician's office, at the neighborhood hospital laboratory, or by a home healthcare worker.

Pharmacologic Agents. Intravenous immunoglobulin (IVIG) is administered to newborn infants diagnosed with either Rh or ABO incompatibility with the goal of reducing or eliminating the need for an exchange transfusion. It is hypothesized that IVIG may interfere with receptors in the reticuloendothelium that are required to induce hemolysis and, thus, reduce the rate of hemolysis. However, while the available evidence shows a significant decrease in the need for exchange transfusions when treated with IVIG, methodological issues limit the strength of the available evidence (Zwiers, Scheffer-Rath, Lopriore, de Haas, & Liley, 2018). The AAP Provisional Committee for Quality Improvement & Subcommittee on Hyperbilirubinemia (Maisels et al., 2004) recommends that affected infants should receive IVIG 500 to 1,000 mg/kg over 2 hours for TSB rising despite intensive phototherapy or if the TSB is within 2 to 3 mg/dL of the exchange transfusion level. It should be noted that promising work with administration of IVIG to women with alloimmunized pregnancies may delay the development of fetal anemia and thus the need for postnatal exchange transfusions (Zwiers et al., 2018).

Phenobarbital is thought to accelerate bilirubin excretion by increasing its uptake and conjugation by the liver and by increasing its excretion by enhancing bile flow. However, no increased benefit is noted that cannot be achieved with phototherapy alone and, thus, it is not routinely used to treat hyperbilirubinemia. At this time, no other medications have been approved in the United States as therapy for inhibition of bilirubin synthesis. There is evidence to suggest that metalloporphyrins may be effective in controlling or reducing hyperbilirubinemia in the term and preterm

infant. Metalloporphyrins are inhibitors of heme oxygenase, the rate-limiting enzyme involved in the degradation of heme to biliverdin, an intermediate in the synthesis of bilirubin (Bhutani et al., 2016) However, further clinical trials are needed before metalloporphyrins may be routinely used to manage hyperbilirubinemia.

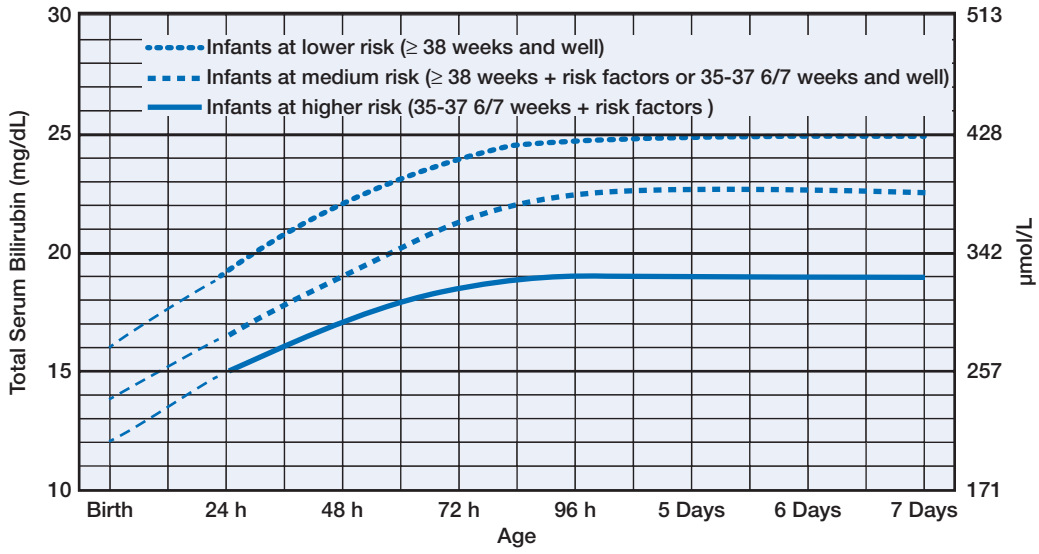
Exchange Transfusion. Once done frequently in NICUs, exchange transfusions are now rarely done and only to treat extreme hyperbilirubinemia or metabolic issues. An exchange transfusion may be necessary if bilirubin levels start to approach those associated with kernicterus despite phototherapy, to protect the CNS status of the jaundiced infant. The objective of this procedure is to remove bilirubin and the antibody-coated RBCs from the newborn's circulation. In addition, exchange transfusion removes some of the circulating maternal antibodies and Rh-positive fetal RBCs while potentially normalizing the Hct. After a single-volume exchange, 75% of the newborn's RBC mass is removed; a double-volume exchange removes 85% to 90% of the cells. However, bilirubin removal is much less effective; only 25% of the infant's total body bilirubin is removed during a double-volume exchange. This probably occurs because the major portion of bilirubin is in the extravascular compartment, an area not affected by the exchange of blood volume. Rebound in bilirubin levels occurs within 1 hour of the exchange, with posttransfusion levels rising as high as 55% of preexchange values.

Although EBF remains the primary condition requiring exchange transfusion, the procedure can also be used to reduce levels of circulating metabolic toxins or exogenous drugs and to reestablish a normal Hct without further volume overload in anemia-induced congestive heart failure. The mortality rate for exchange transfusions is approximately 3 in 1,000 procedures. This rate includes death during the procedure or within 6 hours after its completion but excludes hydropic, kernicteric, or moribund infants (Diab & Luchtman-Jones, 2015; Maisels et al., 2009).

The following criteria are used to determine the need for and timing of exchange transfusions, particularly in infants with EBF (Maisels et al., 2004):

- A cord-blood bilirubin level over 4.5 mg/dL in term infants and 3.5 mg/dL in preterm infants
- A hemoglobin level under 8 g/dL and a bilirubin level over 6 mg/dL within 1 hour of delivery in a term infant
- A hemoglobin level under 11.5 g/dL and a bilirubin level over 3.5 mg/dL within 1 hour of delivery in a preterm infant
- An increase in bilirubin levels by 0.5 mg/dL/hour despite phototherapy
- A bilirubin level over 20 to 25 mg/dL in an uncompromised term infant, 18 mg/dL in the high-risk term newborn, and 10 to 18 mg/dL in the preterm infant, depending on gestational age and condition (Figure 13.9)
- A bilirubin level over 10 to 17 mg/dL in a stressed or very immature preterm infant, over 10 to 12 mg/dL if hypoxia and acidosis are present

- Identical criteria are used to determine the need for repeated exchange transfusion. With more liberal use of phototherapy and appropriate fluid management, exchange transfusions are infrequently necessary (Diab & Luchtman-Jones, 2015).



- **The dashed lines for the first 24 hours indicate uncertainty due to a wide range of clinical circumstances and a range of responses to phototherapy.**
- **Immediate exchange transfusion is recommended if infant shows signs of acute bilirubin encephalopathy (hypertonia, arching, retrocollis, opisthotonos, fever, high pitched cry) or if TSB is ≥5 mg/dL (85 µmol/L) above these lines.**
- **Risk factors - isoimmune hemolytic disease, G6PD deficiency, asphyxia, significant lethargy, temperature instability, sepsis, acidosis.**
- **Measure serum albumin and calculate B/A ratio (See legend).**
- **Use total bilirubin. Do not subtract direct reacting or conjugated bilirubin.**
- **If infant is well and 35-37 6/7 weeks (median risk) can individualize TSB levels for exchange based on actual gestational age.**

FIGURE 13.9 Guidelines for exchange transfusion in infants 35 or more weeks' gestation.

G6PD, glucose-6-phosphate dehydrogenase; TSB, total serum bilirubin.

Source: From Maisels, M. J., Baltz, R. D., Bhutani, V. K., Newman, T. B., Palmer, H., Rosenfeld, W., . . . Weinblatt, H. B. (2004). Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics, 114*, 297–316. doi:10.1542/peds.114.1.297. Copyright © 2004 American Academy of Pediatrics.

Side Effects of Exchange Transfusion

Exchange transfusion can have a marked effect on the cardiovascular status and the intravascular compartment, which is reflected in pressure changes, volume fluctuations, and biochemical balance. Significant morbidities such as apnea/bradycardia, anemia, air embolism, infection, cyanosis, necrotizing enterocolitis, vasospasm, thromboembolism, and death can also occur as a result of an exchange transfusion.

Collaborative Management of the Infant Undergoing an Exchange Transfusion. In addition to the general nursing care required by a sick infant, specific stabilization procedures are necessary for a successful exchange transfusion.

ANEMIA

Pathophysiology

An infant is considered anemic if the hemoglobin or Hct value is more than two standard deviations below normal for his or her gestational age group. During the neonatal period, several abnormalities can evoke states of both acute and chronic anemia in the newborn. These forms of anemia often precede and occur independently of the natural propensity for physiologic anemia that exists as a common entity among all infants, both term and preterm. The conditions that most commonly trigger these pathologic anemias are acute or chronic episodes of hemorrhage, acute or chronic RBC destruction and hemolysis, and blood sampling for laboratory analysis.

Acute Anemia. The physical presentation of acute anemia is more intense than that seen in the chronic form, because the causes of acute anemia are more emergent, life threatening, and disruptive to the homeostasis of the infant (Box 13.2). **Emergency Alert: The resulting cardiovascular collapse, followed closely by respiratory failure, can overwhelm the neonate with only marginal reserves. Immediate intervention and replacement of lost intravascular volume are often required to achieve stabilization.** An infant experiencing an acute anemic episode (hemorrhage being the most common cause) has symptoms reflecting compromise of the cardiorespiratory system: shock, poor peripheral perfusion, poor respiratory effort or respiratory distress, tachycardia, pallor, lethargy, and hypotension. Before signs of acute anemia become apparent, the hemoglobin level must fall precipitously below 12 g/dL.

Acute blood loss results in a recognizable sequence of symptoms based on the volume loss.

- Between 7.5% to 15% volume loss: Little change is noted in heart rate and blood pressure, but stroke volume and subsequent cardiac output are reduced. Peripheral vasoconstriction occurs, resulting in diminished blood flow to the skeletal muscles, gut, and carcass.
- Between 25% to 25% volume loss: Hypotension and shock become apparent. Cardiac output is reduced, and peripheral vasoconstriction is present. Low tissue oxygen levels and acidosis become apparent.

Chronic Anemia. Prolonged, or chronic, anemia may not require rapid intravascular volume expansion, but it is by no means completely benign, as is seen with EBF or chronic twin-to-twin transfusion (Box 13.3). In both of these conditions, infants may require removal of intravascular volume and replacement with a volume of a higher Hct before stabilization is achieved. Because these infants have had considerable time to adjust to chronic blood loss or hemolysis, the changes in vital signs may reflect poor oxygen-carrying capacity rather than hypovolemia. On physical

Box 13.2

CAUSES OF ACUTE ANEMIA IN THE NEWBORN

Obstetric Accidents, Malformations of the Placenta and Cord

- Rupture of a normal umbilical cord
  - Precipitous delivery
  - Entanglement
- Hematoma of the cord or placenta
- Rupture of an abnormal umbilical cord
  - Varices
  - Aneurysm
- Rupture of anomalous vessels
  - Aberrant vessel
  - Velamentous insertion
  - Communicating vessels in multilobed placenta
- Incision of placenta during cesarean section
- Placenta previa
- Abruptio placentae
- Uterine rupture

Occult Hemorrhage Before Birth

- Fetoplacental
  - Tight nuchal cord
- Cesarean section
- Placental hematoma
- Fetomaternal
  - Traumatic amniocentesis
  - After external cephalic version, manual removal of placenta, use of oxytocin
  - Spontaneous
  - Chorioangioma of the placenta
  - Choriocarcinoma
- Twin-to-twin
  - Chronic
  - Acute

Internal Hemorrhage

- Intracranial
- Giant cephalohematoma, subgaleal, caput succedaneum
- Adrenal
- Coagulopathies
- Retroperitoneal
- Gastric
- Ruptured liver or spleen
- Pulmonary

(*continued*)

Box 13.2 (*continued*)

Iatrogenic Blood Loss

Phlebotomy

Injury to internal organs and vessels during placement of medical devices such as chest tube, endotracheal tube, orogastric tube, umbilical and urinary catheters

Surgical blood loss

Source: Modified from Gallagher, P. G. (2015). The neonatal erythrocyte and its disorders. In S. H. Orkin, D. G. Nathan, D. Ginsburg, A. T. Look, D. E. Fisher, & S. E. Lux (Eds.), *Nathan and Oski's hematology and oncology of infancy and childhood* (8th ed., pp. 52–75). Philadelphia, PA: Elsevier.

Box 13.3

CAUSES OF CHRONIC ANEMIA IN THE NEWBORN

Immunity Disorders

- Rh incompatibility
- ABO incompatibility
- Minor blood group incompatibility
- Maternal autoimmune hemolytic anemia
- Drug-induced hemolytic anemia

Infection

- Bacterial sepsis
- Viral infections

Congenital Infections

- Syphilis
- Malaria
- Cytomegalovirus
- Rubella
- Toxoplasmosis
- Disseminated herpes
- Disseminated intravascular coagulation

Macroangiopathic and Microangiopathic Hemolytic Anemias

- Cavernous hemangioma
- Large-vessel thrombi
- Renal artery stenosis
- Severe coarctation of aorta

Iron Deficiency Anemia

Galactosemia

Hereditary Disorders of the Red Cell Membrane

- Hereditary spherocytosis
- Hereditary elliptocytosis
- Hereditary stomatocytosis
- Other rare membrane disorders

Pyknocytosis

Red Cell Enzyme Deficiencies

Most Common are:

- glucose-6-phosphate dehydrogenase deficiency
- pyruvate kinase deficiency
- 5′-nucleotidase deficiency
- glucose-6-phosphate isomerase deficiency

(*continued*)

Box 13.3 (*continued*)

Alpha-Thalassemia Syndrome

Alpha-Chain Structural Abnormalities

Gamma-Thalassemia Syndromes

Gamma-Chain Structural Abnormalities

Source: Modified from Gallagher, P. G. (2015). The neonatal erythrocyte and its disorders. In S. H. Orkin, D. G. Nathan, D. Ginsburg, A. T. Look, D. E. Fisher, & S. E. Lux (Eds.), *Nathan and Oski's hematology and oncology of infancy and childhood* (8th ed., pp. 52–75). Philadelphia, PA: Elsevier.

examination, pallor is usually accompanied by hepatosplenomegaly, a reflection of the body's attempt to compensate for blood loss through extramedullary hematopoiesis. The blood smear may also reflect the long-standing nature of the problem; RBCs appear hypochromic and small, and a greater number of immature RBCs are seen.

Common Causes of Pathologic Anemia in the Newborn

Hemorrhage. Hemorrhage is one of the most common causes of pathologic anemia in the newborn. There are many different types of hemorrhage, but they can be classified into four distinct categories, each of which will be discussed in the text that follows.

Fetal–Maternal Transfusion Caused by Transplacental Hemorrhage. This phenomenon occurs in approximately 50% to 75% of all pregnancies and can be an acute or a chronic process. An estimated 5.6% of pregnancies involve a fetal–maternal transfusion in the range of 11 to 30 mL of blood; another 1% involve an exchange of more than 30 mL. Fetal–maternal transfusions can be verified by the presence of fetal cells in the maternal circulation, which can be detected with the erythrocyte rosette test and the Kleihauer–Betke acid elution test for fetal hemoglobin in maternal blood. The erythrocyte rosette test specifically detects fetal RBCs. The Kleihauer–Betke test consists of an acid wash of a maternal blood smear followed by staining. Fetal hemoglobin resists elution from intact RBCs in an acid solution. Intact cells containing fetal hemoglobin can be distinguished microscopically, when stained, from adult erythrocytes. The presence of stained erythrocytes suggests contamination of maternal blood by fetal blood. This test is useful in identifying fetal RBCs in the mother's blood as long as no underlying condition increases the amount of fetal hemoglobin in the mother's blood.

Twin-to-Twin Transfusion. This phenomenon, which can be both acute and chronic, occurs in 15% to 33% of all monochorionic (monozygotic) twins, in which the placentas tend to be fused. The anastomosis is usually between an artery of one placenta and a vein of the other, although vascular connections may be artery to artery or vein to vein. In the chronic form of twin-to-twin transfusion, the size difference between twins can be helpful in determining the donor and the recipient. When the weight difference exceeds 20%, the smaller twin is always the donor. When the weight difference is less than 20%, either twin may be the donor. In such cases, Hct values prove useful in determining the donor and the recipient. The donor twin is anemic, and the blood count reflects increased hematopoiesis, as evidenced by an elevated reticulocyte count and increased numbers of immature RBCs. The recipient develops polycythemia but can exhibit signs of congestive heart

failure and pulmonary or systemic hypertension. Laboratory data usually show a difference of 5 g/dL between donor and recipient hemoglobin values. Stillbirths are common in twin-to-twin transfusion, and both twins are at risk.

Obstetrical Accidents. Many obstetrical problems, especially those that occur before labor and delivery, can result in chronic as well as acute blood loss. Long-standing problems, such as placenta previa or partial abruption, usually result in anemia. However, acute hemorrhage rather than anemia is the case in problems that occur at the time of delivery. Examples are severe abruption, severing of the placenta during cesarean section, uterine rupture, or umbilical cord rupture as a result of sudden tension on a short or tangled cord. A tight nuchal cord can reduce blood volume in a newborn by approximately 20%. Holding a newly delivered infant above the placenta can also reduce the Hct and blood volume because of the gravitational drainage of blood from the newborn into the placenta.

Internal Hemorrhage. A drop in the Hct during the first 24 to 72 hours that is not associated with hyperbilirubinemia is usually attributed to internal hemorrhage. Bleeding can occur in various parts of the body secondary to birth trauma or preexisting anomalies. The areas of potential hemorrhage in the head include the subdural, subarachnoid, intraventricular, intracranial, and subgaleal spaces. Infants can lose an estimated 10% to 15% of their blood during an intraventricular or intracranial hemorrhage. In cases of traumatic delivery or vacuum extraction, extensive scalp bleeding can result in the subgaleal space as a result of the emissary vein rupturing. Significant blood loss can occur as the subgaleal space can hold up to 240 mL of blood. Blood loss in the head can be estimated by measuring the increase in the head circumference. Each centimeter of increase represents an estimated 38 mL of blood lost from the intravascular compartment. Hemorrhage into the liver, kidneys, spleen, or retroperitoneal space can also occur in association with traumatic and breech deliveries.

Hepatic rupture occurs in approximately 1.2% to 5.6% of stillbirths and neonatal deaths; half of the hemorrhages are subcapsular. Infants with this disorder tend to be stable for 24 to 48 hours and then suddenly deteriorate. This deterioration seems to coincide with rupture of the capsule and hemoperitoneum. Hepatic rupture carries a poor prognosis, but rapid surgery preceded by multiple transfusions can save the infant. Splenic rupture is associated with severe EBF and should be suspected at the time of exchange transfusion if the central venous pressure is low rather than elevated. Signs of splenic rupture include scrotal swelling and peritoneal effusion without free air. Adrenal hemorrhage is seen more often in the infant of a diabetic or prediabetic mother and is characterized by a flank mass with bluish discoloration of the overlying skin.

RED BLOOD CELL DESTRUCTION AND HEMOLYSIS

Maternal–Fetal Blood Group Incompatibilities

Isoimmunization, as in ABO and Rh incompatibility, accounts for most cases of neonatal hemolysis. A reduced RBC life span caused by hemolysis is usually associated with a rise in the bilirubin level, 1 g of hemoglobin yielding 35 mg of bilirubin. Infants who have received intrauterine transfusions or exchange transfusions for blood group incompatibilities are predisposed to a hyporegenerative anemia that develops within the first few months of life. The pathophysiology is considered to be bone marrow suppression, possibly as a result of the increased amount of hemoglobin A received during the blood transfusions.

Acquired Defects of the Red Blood Cells. This hemolytic problem is seen in bacterial sepsis and viral infections, especially congenital infections such as syphilis, rubella, toxoplasmosis, CMV, or herpes, once referred to as TORCH, as well as human immunodeficiency virus and hepatitis. Drug-induced RBC destruction, caused by either maternal ingestion or direct administration of the drug to the newborn, is another common cause of hemolysis. An example of this would be the hemolysis that could occur with administration of iron supplements to an infant with vitamin E deficiency.

Congenital Defects of the Red Blood Cells. Defects resulting in destruction of the RBCs can involve the cell membrane, enzymatic system, or hemoglobin component, as in glucose-6-phosphate dehydrogenase (G6PD) deficiency, thalassemia, and hereditary spherocytosis. Although these conditions can cause hemolysis in the newborn period, they are rare diseases.

Blood Sampling. Blood loss that occurs secondary to sampling is one of the two most frequent causes of chronic anemia in infants, the other being physiologic anemia of the newborn and premature infant. For sick term infants, phlebotomy losses can account for 4% to 5% of blood volume, and in premature infants weekly phlebotomy losses in the first 4 weeks of life average 15% to 30% of their total blood volume (Widness, 2008). For those infants that had DCC, the DCC could lessen the amount of anemia, but a study by Elimian et al. (2014) demonstrated that this was not the case for premature neonates. **Quality and Safety: Prudent blood sampling may eliminate unnecessary blood volume depletion and reduce the need for replacement transfusion therapy.** Accurate recording of blood lost to sampling can prove beneficial in the assessment of a sick infant's circulatory status and volume needs. However, perfusion status and Hct values may be better determinants of the need for volume expansion or blood transfusions.

Differential Diagnosis

History. Acute and chronic anemia often can be distinguished from each other and from other problems by analyzing the family history for anemia or jaundice. The maternal history should be carefully examined for evidence of drug ingestion that may affect RBC life span or production, bleeding during the pregnancy or labor, or other incidents surrounding the delivery that may contribute to blood loss in the newborn.

Laboratory Findings. The type of anemia often can be identified on the basis of laboratory studies that evaluate RBC content and form.

- Hct and hemoglobin levels can define the type as well as the degree of anemia. Blood loss during acute hemorrhage is rapid, with little evidence of the compensatory hematopoiesis seen in chronic anemia. RBCs are of normal size and have a normal hemoglobin mass, and no significant increase is seen in the number of immature RBCs. Hemoglobin values initially may not reflect hemorrhage because the intravascular volume contracts and masks volume loss. It may take 3 to 4 hours for intravascular equilibration to occur before the hemoglobin accurately reflects the extent of the hemorrhage. The site of hemoglobin or Hct sampling is important for obtaining accurate information, because capillary sticks on an infant in shock reflect venous stasis. A more accurate sample at this time would be from an arterial or venous source.
- Reticulocyte counts are useful in differentiating chronic and acute forms of anemia. Increased numbers of immature RBCs reflect the degree of hematopoietic activity in response to anemia. Increased hematopoiesis requires a time lapse between the occurrence of anemia and stimulation of the hematopoietic centers.

- Peripheral blood smears are helpful in evaluating iron content and the size and shape of the RBC, which vary in different forms of anemia.
- Blood typing, Rh determination, and Coombs testing can help identify blood group incompatibilities as causes of anemia.

Treatment

Collaborative Management of the Infant With Acute Anemia. The following measures are used to stabilize the condition of an infant with acute anemia:

- Basic resuscitation of the infant experiencing precipitous blood loss often includes stabilization of the airway by means of intubation and ventilation.
- Rapid line placement for fluid replacement, volume expansion, and blood sampling may require use of the umbilical vein or artery. Central venous pressure measurements can be helpful in assessing the degree of volume loss and the amount of replacement needed.
- If acute volume expansion is required, normal saline is the volume expander of choice at 10 to 20 mL/kg. If time allows, fresh frozen plasma or low-titer, type O-negative blood can be used at the dosing of normal saline until a type and cross-match replacement is available. In an emergency situation, blood taken from the fetal side of the placenta after it is delivered in a sterile manner can also be infused into the neonate. Failure to respond may indicate continuing internal hemorrhage.
- After the infant's condition has been stabilized, laboratory tests and a physical examination should be performed to determine the cause of the anemia and to rectify the problem.
- Examination of the placenta and maternal blood sample testing for fetal hemoglobin may prove useful in determining the cause of the blood loss.

Emergency Alert: Anemia in the premature infant is a complication of being born prematurely or physiologic anemia, as well as phlebotomy losses related to lab draws. Anemia can be lessened by questioning the necessity of standing labs with the practitioner to eliminate unnecessary labs.

As with all newborns, the principles of care (provision of warmth, monitoring of vital signs, ongoing assessment, and accurate determination of intake and output) are essential to the well-being of the infant who has suffered acute blood loss. After initial stabilization, nursing care must include modifications that either eliminate recurrence of precipitous events or prevent further blood loss. Providing safe care to such infants requires adequate knowledge of the principles and procedures involved in volume expansion and the use of blood products. A review of the use of blood products can be found at the conclusion of this chapter.

Collaborative Management of the Infant With Chronic Anemia. The major focus of therapy for the infant with chronic anemia is control or elimination of the cause of the anemia. Several forms of chronic anemia in term and preterm infants are linked to dietary deficiencies that can be eradicated by replacement therapy. Chronic forms of anemia requiring symptomatic therapy can also be treated with transfusion therapy and erythropoietin.

Dietary Supplementation. The three major dietary factors that affect RBC production are iron, folate, and vitamin E. Because all three increase in amount with increasing gestational age, premature birth predisposes the immature infant to anemia as a result of insufficient stores.

Without the benefit of iron supplementation, the hematopoiesis necessary to maintain a normal hemoglobin level depletes the infant's iron reserves by the time birth weight is doubled. Various factors can further contribute to iron deficiency anemia, such as low birth weight, low initial hemoglobin levels, and blood loss through trauma, hemorrhage, or sampling. In the term infant, exhaustion of iron reserves normally occurs by 20 to 24 weeks postnatal age, but this happens much earlier in the preterm infant. Iron stores needed for hemoglobin production are present in insufficient quantities at birth in the premature infant, making supplementation necessary during the first 2 to 4 months to prevent iron deficiency anemia.

In any gestational age group, iron depletion first becomes evident in reduced serum ferritin levels (serum ferritin being a measure of accumulated iron stores) and in the disappearance of stainable iron from the bone marrow. A subsequent reduction in the mean corpuscular volume of the RBC is followed by a drop in the hemoglobin level. Although prophylactic iron supplementation does not prevent the initial fall in hemoglobin, the administration of 1 mg/kg/day for exclusively breastfed infants or breastfed infants that receive 50% of their nutrition through breast milk starting at 4 months of age, and 2 mg/kg/day of supplemental iron, should supply preterm infants starting at 1 month of age with adequate reserves; 2 to 4 mg/kg/day is recommended in iron-deficient infants or those receiving erythropoietin. Term infants on formula do not need supplementation as commercial formula has iron (Baker et al., 2010).

Folate is the generic description for folic acid and its related compounds. Folate is a component of the B-complex vitamins involved in the maturation of RBCs, particularly the synthesis of DNA, which controls nuclear maturation and division. Because bone marrow is one of the body's faster growing and more proliferative tissues, folic acid deficiency diminishes its ability to produce RBCs, resulting in a megaloblastic anemia.

High amounts of folate are present at birth in both term and preterm infants, but these levels drop rapidly, especially in LBW infants. It is estimated that approximately 68% of infants weighing less than 1,700 g have subnormal levels of folate at 1 to 3 months of age. However, only a few infants actually develop anemia. Human milk and soy-based products contain an adequate amount of natural folate, but commonly used commercial products must be artificially enriched. Premature infant formulas are adequately enriched to satisfy a premature infant's folate needs provided that intake is sufficient. Because folate is absorbed in the duodenum and jejunum, any disease or medication that affects the absorptive surface of these areas can impair folate absorption (Gallagher, 2015).

Vitamin E, an antioxidant, is valuable in protecting the RBC membrane from destruction due to lipid peroxidation. Deficiency of this nutrient shortens the life span of the cell by exposing the unprotected, unsaturated membrane lipids to peroxidation and hemolysis. Infants are born in a state of relative vitamin E deficiency that is more intense in the smaller and more premature infants. Vitamin E is required in increasing amounts as the intake of polyunsaturated fatty acids increases. Deficiency becomes apparent in infants of birth weights less than 1,500 g at approximately 4 to 6 weeks of age, resulting in decreased hemoglobin levels ranging from 7 to 10 g/dL. The administration of iron supplementation in the presence of vitamin E deficiency will intensify the hemolytic response. Signs and symptoms, as with many neonatal diseases, mimic those of other disease entities that occur in the neonatal period. One of the more obvious symptoms is edema of the feet, lower extremities, and scrotal area. The appearance of the RBCs may vary, but abnormalities usually include fragmented or irregularly shaped cells, presence of spherocytes, and thrombocytopenia. Infant formulas are now enriched with adequate amounts of vitamin E, provided formula intake is sufficient.

Transfusion Therapy. In the past, of all preterm infants admitted to a NICU, approximately 90% received one transfusion in the first 6 weeks of life; 50% received cumulative transfusions in excess of their total circulating RBC mass. Today, transfusions have declined as the result of the improved treatment and prevention of neonatal lung disease, the reduction of blood loss from gas and chemistry analysis, early protein and adequate iron supplementation, as well as the use of transfusion guidelines (Gallagher, 2015). In determining which infants may need subsequent transfusions after the first 2 weeks of life, gestational age of less than 30 weeks is the best predictor, regardless of severity of illness, number of transfusions during the first week, complications, or Hct level at birth. Only 14% of infants of more than 30 weeks' gestation require transfusions after 2 weeks of age.

Although a critically ill infant is generally maintained with an Hct level above 40%, the benefits of transfusion therapy in the convalescent infant remain controversial. When the effects of transfusion therapy in the convalescent infant were studied, the elimination of symptoms attributed to anemia was not a consistent finding. In premature infants with an Hct level below 30%, apnea, bradycardia, dyspnea, feeding difficulties, poor weight gain despite good calorie intake, lethargy, tachypnea, tachycardia, and increased cardiac output and oxygen consumption appear to be relieved by transfusion therapy in some studies. There appears to be no overall relationship between Hct values and physiologic symptoms such as apnea, bradycardia, or changes in heart and respiratory rates, nor does abatement of these symptoms follow transfusion therapy (Gallagher, 2015).

In light of the controversy surrounding transfusions, evidence of impaired tissue oxygenation remains the ultimate criterion for the use of blood products. Measurement of lactic acid levels may prove helpful in determining which infants may benefit from transfusion therapy. When the oxygen-carrying capacity of hemoglobin is insufficient for tissue needs, anaerobic metabolism occurs, leading to excess production of lactic acid. Monitoring of lactic acid levels and transfusing only those infants with elevated levels may aid in establishing more sound criteria for transfusion therapy.

Several methods of blood preparation and use have been evaluated to minimize donor exposure and reduce the potential for transmitted disease. Studies suggest that packed RBCs with a shelf life of more than 5 days, and up to 42 days, are safe for use in neonatal transfusions (Nunes dos Santos & Trindade, 2011). This finding, combined with the use of a sterile connection device that allows multiple aseptic entries into a unit of blood, would permit the use of a designated unit for each infant at risk for multiple transfusions, thereby significantly reducing donor exposure (Nunes dos Santos & Trindade, 2011). The desire to limit donor exposure must inevitably be balanced by the limited availability of banked blood. Multiple users on a blood unit may reduce wastage but may possibly expose an infant to multiple donors.

Blood administered to the newborn is often irradiated, which causes cell membrane disruption and potassium leakage from the cell. The decision by the U.S. Food and Drug Administration to change its recommendations for the maximum storage time of irradiated blood from 42 to 28 days affects the length of use of a designated unit. Although older blood appears to be safe to administer, it is not recommended for rapid transfusions, administration of large aliquots, exchange transfusions, or treatment of coagulopathies.

The establishment of transfusion criteria can effectively minimize donor exposure. These guidelines help determine which infants would benefit from transfusion on the basis of symptoms, Hct value, and severity of illness (Fasano, Said, & Luban, 2015; Nunes dos Santos & Trindade, 2011).

Recombinant Human Erythropoietin Therapy. Cloning of the human erythropoietin (HuEPO) gene in 1985 resulted in the production of large amounts of HuEPO for use as an exogenous stimulant of erythroid progenitor cells in patients with anemia. HuEPO acts primarily on CFU-E, derivatives of the hematopoietic stem cells in the bone marrow and the precursors of the RBCs (Figure 13.9). Studies from the United States and England have shown the use of recombinant erythropoietin to be an effective replacement for transfusion therapy in raising the hemoglobin level in hyporegenerative anemia and end-stage renal disease. Further studies of preterm infants have demonstrated that HuEPO maintains the Hct level during the phase of normal anemia of the premature infant, with good proliferation of erythroid progenitor cells in response to HuEPO.

HuEPO attained recognition as a standard of care for anemia of prematurity, because several clinical trials established its effectiveness in reducing both the number of transfusions and the cumulative volume of transfused blood needed in treated patients. A Cochrane review of literature by Aher and Ohlsson (2012) showed in comparing early versus late erythropoietin usage for preventing RBC transfusion for preterm and/or LBW infants that early erythropoietin (before 8 days of age) did not significantly reduce the use of one or more RBC transfusions or the number of transfusions per infant compared to late administration of erythropoietin. They did find a statistically significant increased risk of retinopathy of prematurity of any stage in those in the early treatment groups as well as for retinopathy greater than stage 3, which is concerning. Aher and Ohlsson also looked at late erythropoietin usage to prevent RBC transfusion in preterm and/or LBW infants. In this review they found that the administration of erythropoietin at 8 days or after did decrease the use of one or more RBC transfusions and the number of transfusions per infant. There was no decrease or increase in clinically important adverse outcomes with the late use of erythropoietin. They noted that donor exposure was not reduced as all infants had had a transfusion prior to the administration of the erythropoietin.

The use of erythropoietin in treating anemia of prematurity varies according to the physician and institution where the neonate is hospitalized. If used, the usual response in preterm infants given HuEPO is an increase in blood levels of erythropoietin and reticulocytes, as well as RBC volume, 2 to 3 weeks after initiation of therapy. The accepted dosage of erythropoietin is 150 to 1,500 U/kg/week divided into two to five doses. The commonly used dose is 250 U/kg/dose. The dose is given subcutaneously in rotating sites three times a week for 10 doses and should have supplemental iron given (Lexicomp Online, 2018).

HuEPO has been evaluated for its effectiveness as an alternative to transfusion therapy for treatment of anemia in premature infants caused by (a) blood sampling, with administration beginning within the first 2 days of life, (b) physiologic anemia of prematurity, with therapy starting at 1 to 4 weeks of age, and (c) anemia of bronchopulmonary dysplasia, with treatment starting at 3 months of age.

Serum ferritin levels decline rapidly after initiation of HuEPO therapy in infants with normal pretreatment ferritin levels, despite prophylactic iron supplementation of 2 mg/kg/day. This predisposition to the development of iron deficiency anemia underlines the need for increased iron supplementation in infants treated with HuEPO. Also documented as side effects of HuEPO therapy are transient thrombocytosis shortly after the initiation of therapy and transient neutropenia. The transient neutropenia can last as long as 2 months after discontinuation of therapy. It has been postulated that this phenomenon is due to a stimulant effect of HuEPO on megakaryocyte progenitors and a negative

effect on granulocyte–monocyte progenitor cells. Before HuEPO was proven effective in raising Hct levels, its use was projected to eliminate the need for one third of all transfusions in premature infants.

PHYSIOLOGIC ANEMIA OF THE NEWBORN AND ANEMIA OF THE PREMATURE INFANT

Shortly after birth, the physiologic regulator of RBC production, erythropoietin, falls to barely perceptible levels because the relative intrauterine hypoxia that stimulated its release in-utero is no longer present. Erythropoietin levels remain low until another hypoxic stimulus occurs, one created by the normal drop in the hemoglobin level that marks physiologic anemia of the newborn. This drop in the hemoglobin level is due to decreased marrow production of RBCs secondary to diminished circulating erythropoietin levels, a shorter life span of the neonatal RBC with destruction of fetal hemoglobin, and hemodilution caused by growth.

The drop in hemoglobin that prompts the postnatal rise in erythropoietin directly correlates with the infant's gestational age and birth weight (Figure 13.11). The smaller and more immature infant reaches a lower nadir at an earlier postnatal age. The hemoglobin level in the term newborn reaches a nadir of 11.4 g/dL ±0.9 in the first 2 to 3 months of life and plateaus at this level for approximately 2 more months before it gradually increases. Although there is no significant difference in cord-blood hemoglobin levels between term infants and preterm infants born after 32 weeks' gestation, the drop in hemoglobin occurs earlier in the preterm infant, is more precipitous, and reaches a lower nadir. Starting at 2 weeks of age, the preterm infant has a drop in hemoglobin of 1 g/dL/week for the first several weeks; the nadir at 6 to 8 weeks of age is 2 to 3 g/dL lower than that of the term infant. An infant weighing 1,000 to 1,500 g at birth will have a mean hemoglobin nadir of 8 g/dL at 4 to 6 weeks of age.

Infants who have undergone exchange transfusion or multiple transfusions also have a greater fall in their hemoglobin level in the first 3 months of life. This phenomenon theoretically may be due to improved oxygen delivery to tissue associated with the replacement of fetal hemoglobin with adult hemoglobin. Adult hemoglobin has less affinity for oxygen because of the structural difference of the globin portion of the hemoglobin molecule. This, coupled with the increased amount of 2,3-disphosphoglycerate present in the blood, allows adult hemoglobin to release oxygen to the tissue more easily. Improved tissue oxygenation effectively lowers serum erythropoietin levels (Figure 13.11), resulting in decreased RBC production. Consequently, an infant undergoing intrauterine transfusion, exchange transfusion, or frequent postnatal transfusions has improved tissue oxygenation and a decreased erythropoietin level.

The switch in the predominant site of erythropoietin production during fetal life from the liver to the kidneys occurs concurrently with the change in hemoglobin to a more mature form. Hepatic production of erythropoietin in response to hypoxia is not as rapid as the kidneys' response, an adjustment that actually spares the fetus from polycythemia in-utero. However, persistence of this hepatic pathway after premature birth may explain why the premature infant's Hct values reach a lower nadir that persists longer compared with the term infant. Although erythropoietin levels are reduced in the early newborn period, the erythroid progenitor cells in the bone marrow are exceedingly sensitive to erythropoietin and respond rapidly as blood levels increase. The normal erythropoietin level in infants beyond the newborn period is 10 to 20 U/mL.

Treatment

Physiologic anemia does not usually require any form of treatment. With good nutrition, the hemoglobin level in the term infant should start to rise by 3 months of age. With adequate nutrition and iron supplementation, the hemoglobin level in the preterm infant should start to increase by 5 months of age, eventually attaining hemoglobin values comparable to those of the term infant. Controversy remains though for the preterm infant with symptomatic anemia of prematurity on how to best treat the infant.

The controversy is on the use of blood transfusion of packed red blood cells (PRBC) versus recombinant erythropoietin (EPO) therapy. PRBC transfusion has been the mainstay of treatment for symptomatic anemia of prematurity, but with increasing evidence on complications of transfusions and concern of exposure to multiple donors the use of it has been questioned. Complications associated with blood transfusions are infections, fluid overload and electrolyte imbalances, exposure to plasticizers, hemolysis, hypoglycemia, hyperkalemia, hypocalcemia, transfusion reactions

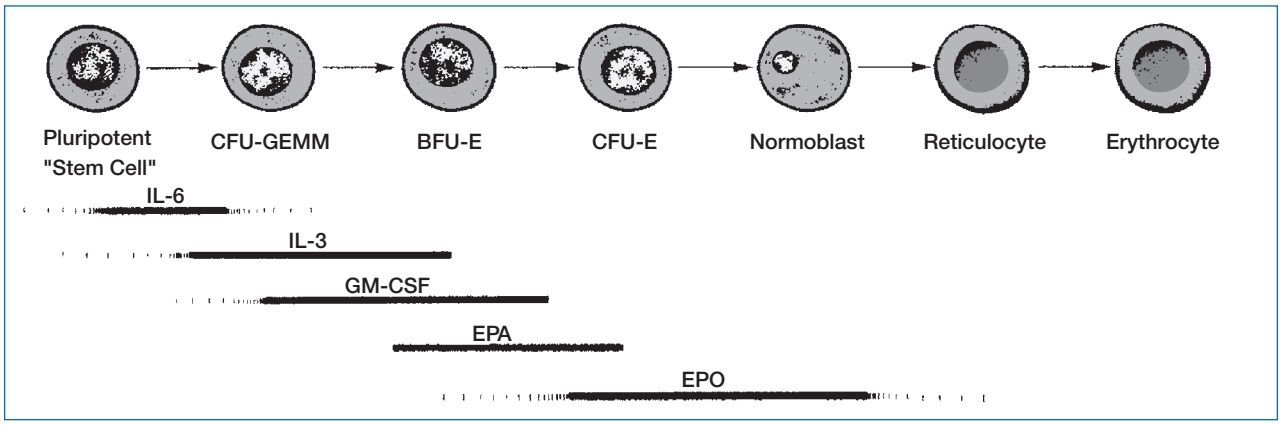


FIGURE 13.10 The principal action of human recombinant erythropoietin is on the derivatives of the hematopoietic stem cells in the bone marrow that have been designated erythrocyte colony-forming units (CFU-E), the precursors of the red blood cell (RBC).

BFU-E, erythrocyte burst-forming units; CFU-GEMM, colony-forming units—granulocytes, erythroid cells, macrophages, and megakaryocytes; EPA, erythroid potentiating activity; EPO, erythropoietin; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL-3, interleukin-3; IL-6, interleukin-6.

Source: From Christensen, R. (1989). Recombinant erythropoietic growth factors as an alternative to erythrocyte transfusion for patients with anemia of prematurity. *Pediatrics, 83*(5), 793–796. doi:10.1016/S0022-3476(05)82671-X

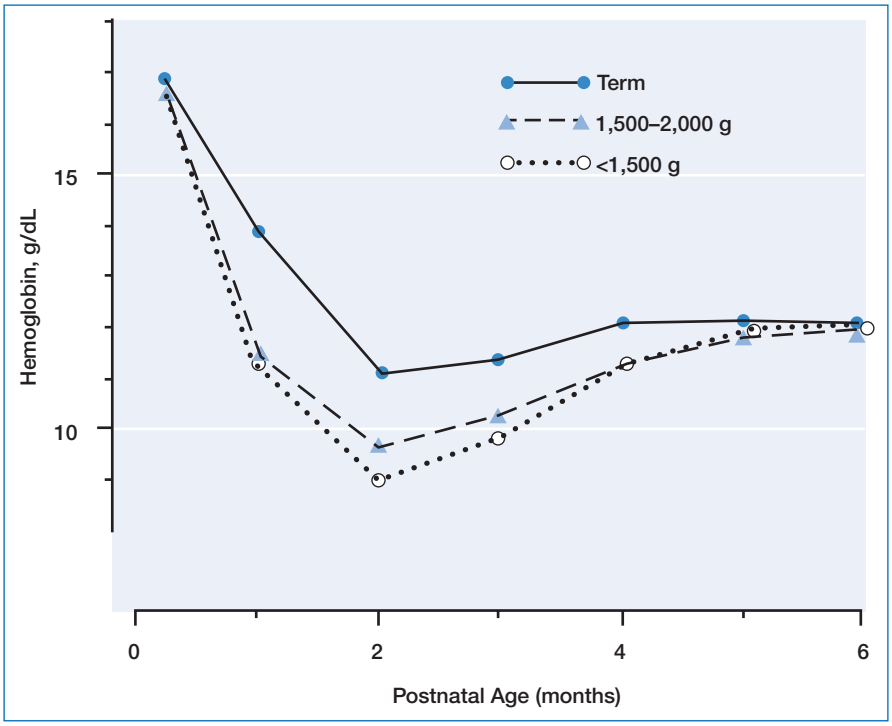


FIGURE 13.11 Gestational age and birth weight are directly correlated with the timing of the postnatal drop in hemoglobin and with the nadir of the drop. Shown here are the differences between term infants and two groups of preterm infants, one weighing 1,500 to 2,000 g and the other less than 1,500 g.

Source: From Brown, M. (1988). Physiologic anemia of infancy: Normal red cell values and physiology of neonatal erythropoiesis. In J. Stockman & C. Pochedly (Eds.), *Developmental and neonatal hematology* (pp. 249–274). New York, NY: Raven Press.

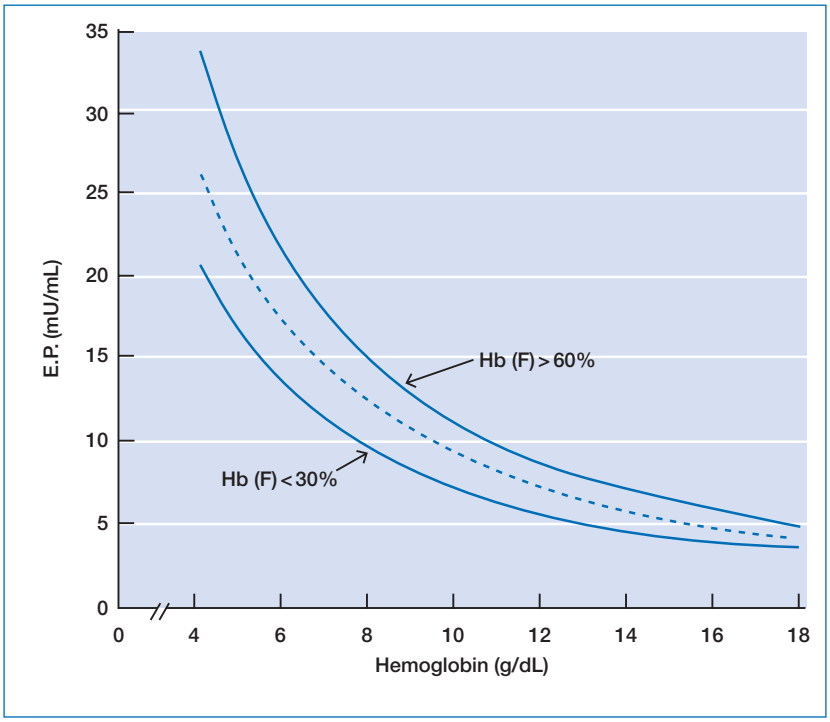


FIGURE 13.12 Because of the differences in oxygen affinity between adult and fetal hemoglobin, variations in the percentage of available fetal hemoglobin (hemoglobin F) affect erythropoietin levels. Improved oxygen uptake but decreased unloading at the tissue level is associated with hemoglobin F. Therefore, the stimulus for erythropoietin production is diminished with lower concentrations of hemoglobin F (<30%). With higher concentrations (60%) of hemoglobin F, the stimulus response is an increase in erythropoietin production. At identical total hemoglobin levels, the stimulus for erythropoietin production is increased whenever the percentage of hemoglobin F exceeds the adult norm.

Source: Adapted from Stockman, J., Garcia, J. F., & Oski, F. A. (1977). The anemia of infancy and the anemia of prematurity: Factors governing the erythropoietin response. *New England Journal of Medicine, 296*, 647. doi:10.1056/NEJM197703242961202.

(though rare), necrotizing enterocolitis, and intraventricular hemorrhage (Cassady, 2016; Fasano et al., 2015).

An alternative to blood transfusion is the use of HuEPO to prevent anemia. Premature neonates have physiologically lower levels of EPO and use pharmacologically available HuEPO to stimulate bone marrow production of RBCs and decrease the number of blood transfusions. As stated earlier, a Cochrane review in 2012 compared early (before 8 days of life) versus late EPO (on or after 8 days of life) usage in premature infants. The early group had decreased RBC transfusions and donor exposures, but it did not eliminate the transfusions and did not affect mortality or morbidities, except to increase the incidence of retinopathy of prematurity. The late group decreased the number of RBC transfusions, but not total blood volume. In both studies infants had received RBC transfusion prior to the administration of EPO. The authors concluded that efforts should be made to limit transfusions and donor exposure in the first days of life. Stable larger infants respond better to EPO than more extremely premature infants. It is important to note that in 2007 the Food and Drug Administration (FDA) put out a Black Box warning for the use of EPO in the adult population due to the increased risk of death, myocardial infarctions, stroke, venous thrombosis, and cancer progression. There are pros and cons to each therapy and the controversy continues. The question of which one is best has not yet been answered conclusively.

Polycythemia

Pathophysiology. Polycythemia is defined as a peripheral venous Hct level over 65%, or a Hct level two standard deviations above the mean. Polycythemia occurs in 4% to 5% of the total population of newborns, in 2% to 4% of term infants appropriate for gestational age, and in 10% to 15% of infants either small or large for gestational age. It has not been observed in infants of less than 34 weeks' gestation. Although the fetus lives in a low-Po_2 environment that should induce a polycythemic response, it protects itself by keeping Hct levels below 60%. This may be a function of slower fetal hepatic response to hypoxia compared with rapid renal response after birth. The average Hct on the first day of life is approximately 50% in the term infant and the preterm infant of more than 32 weeks' gestation and 45% in the preterm infant of less than 32 weeks' gestation. During the first 4 to 12 hours of life, hemoglobin and Hct values rise due to fluid shifts and then equilibrate, especially in infants receiving large placental transfusions.

The choice of sampling site can affect Hct values considerably, particularly during the early newborn period when peripheral circulation may be somewhat sluggish. Infants younger than 1 day of age either lack or have diminished cutaneous vasoregulatory mechanisms that reduce peripheral perfusion. Capillary blood sampling sites will have the highest Hct, then blood from a peripheral site, with central blood having the lowest Hct. Compared with venous samples, the Hct levels of capillary samples are 5% to 15% higher, and those of umbilical vessel or arterial samples are 6% to 8% lower.

The main concern with polycythemia is that it can impair peripheral circulation by increasing blood viscosity and reducing the flow rate. As blood viscosity increases, vascular resistance increases in the peripheral circulation and the microcirculation of the capillaries throughout the body. Three major factors determine blood viscosity: Hct, plasma viscosity (osmolality), and deformability of the RBCs. With Hct levels below 60% to 65%, blood viscosity increases in a linear fashion, but viscosity exponentially increases at higher Hct levels (Diab & Luchtman-Jones, 2015).

Variations in the components of plasma affect blood viscosity independent of the Hct. Abnormal composition of plasma protein, electrolytes, and other metabolites can either decrease or increase plasma viscosity. Such an increase in the presence of a high Hct level further increases blood viscosity and reduces the blood flow rate. The ability of cells to modify their shape to successfully traverse the peripheral vascular bed and microcirculation also affects the blood flow rate. The degree of deformability of the cell determines its ability to pass through small vascular spaces; the greater the deformability of the cell, the quicker its passage. Less deformable cells can increase blood viscosity by occluding small vessels, causing sludging in the microcirculation that can lead to thrombosis and tissue ischemia.

The two major types of polycythemia are (1) the active form, which is caused by the production of an excess number of RBCs in response to hypoxia and other poorly defined stimuli; and (2) the passive form, which is caused by RBC transfusion to an infant secondary to maternal–fetal transfusion, twin-to-twin transfusion, or DCC (Diab & Luchtman-Jones, 2015).

Active Polycythemia. Tissue hypoxia, regardless of the cause, elicits an increase in erythropoietin that stimulates RBC production. In the fetus, erythropoietin is produced initially by the liver and then by the kidneys, the adult production site. The kidneys' potential to release erythropoietin is active by 34 weeks' gestation. At this time, a renal erythropoietic factor reacts with a substance in the plasma to produce erythropoietin, the RBC stimulating factor. Hypoxia of the tissues adjacent to the renal tubules, where erythropoietin is produced, is the potent stimulator of this factor's release.

Many factors can lead to tissue hypoxia associated with the active form of polycythemia. These factors include the following:

1. Maternal factors that result in reduced placental blood flow
   - Pregnancy-induced hypertension
   - Older maternal age
   - Maternal renal or heart disease
   - Severe maternal diabetes (Hct values of 64% or higher are found in 42% of infants of a diabetic mother and 30% of gestational infants of a diabetic mother)
   - Oligohydramnios
   - Maternal smoking (the mechanism is thought to be production of carbon monoxide that crosses the placenta and induces a state of tissue hypoxia in the fetus)
2. Placental factors
   - Placental infarction
   - Placenta previa
   - Viral infections, especially TORCH
   - Postmaturity
   - Placental dysfunction that results in a small-for-gestational-age (SGA) infant
3. Fetal syndromes
   - Trisomies 13, 18, and 21
   - Beckwith–Wiedemann syndrome (Diab & Luchtman-Jones, 2015; Kandasamy, 2017)

Passive Polycythemia. Passive polycythemia is a result of increased fetal blood volume caused by maternal–fetal transfusion, or twin-to-twin transfusion, with one twin being polycythemic and the other anemic. A diagnosis of maternal–fetal transfusion can be considered when (a) the infant's blood is found to contain larger amounts than expected of adult hemoglobin, IgA, or IgM; (b) RBCs in the infant's blood have maternal blood group antigens, if the mother's and the infant's blood groups are different; or (c) XX cells are found in an XY infant. In twin-to-twin transfusion, morbidity and mortality are comparable in both groups of affected infants, with one twin being anemic and the other polycythemic.

Clinical Manifestations. Symptoms of polycythemic hyperviscosity, which are usually evident within the first few days

after birth, reflect compromise of various organ systems. The most commonly seen findings include the following:

1. Neurological symptoms
   - Lethargy or irritability
   - Hypotonia
   - Tremulousness
   - Exaggerated startle
   - Poor suck
   - Vomiting
   - Seizures
   - Apnea
2. Cardiovascular symptoms
   - Plethora
   - Cardiomegaly
   - Electrocardiographic changes (right and left atrial hypertrophy, right ventricular hypertrophy)
3. Respiratory symptoms
   - Respiratory distress
   - Central cyanosis
   - Pleural effusions
   - Pulmonary congestion and edema
   - Persistent pulmonary hypertension of the newborn
4. Hematological symptoms
   - Hyperbilirubinemia
   - Thrombocytopenia
   - Elevated reticulocyte level
   - Coagulopathies
   - Hepatosplenomegaly
   - Renal and/or cerebral vein thrombosis
5. Gastrointestinal symptoms
   - Poor feeding
   - Necrotizing enterocolitis
6. Genitourinary symptoms
   - Oliguria
   - Hematuria
   - Proteinuria
7. Metabolic symptoms
   - Hypocalcemia
   - Hypoglycemia (Diab & Luchtman-Jones, 2015; Kandasamy, 2017)

Hypoglycemia found in conjunction with polycythemia can be a reflection of (a) increased glucose consumption by an overabundant number of RBCs; (b) increased cerebral extraction of glucose secondary to hypoxia; (c) a state of hyperinsulinemia caused by increased erythropoietin levels; or (d) decreased hepatic glucose production as a result of sluggish hepatic circulation. Hyperbilirubinemia associated with polycythemia is a reflection of increased by-products of RBC destruction.

The complications of polycythemia center around the increased resistance to blood flow related to hyperviscosity; blood flow to all organ systems is impaired by sluggish circulation. Pulmonary blood flow can be dramatically compromised, resulting in pulmonary hypertension, retained lung fluid, and respiratory distress syndrome. Taxation of the heart by an increased vascular load can lead to congestive heart failure and left to right shunting across the foramen ovale or ductus arteriosus. **Emergency Alert: Sludging of blood in the microcirculation of the kidneys can lead to renal vein thrombosis and renal failure.** Impairment of blood flow to the bowel can lead to necrotizing enterocolitis (Kandasamy, 2017).

Treatment. Although most infants with polycythemia are asymptomatic or minimally symptomatic, the Hct level and the presence of symptoms, even if minimal, should form the basis of treatment. Majority of neonates will need to be observed for cardiac and respiratory status, have Hct drawn every 6 to 12 hours, and observed for signs of the problems noted in the previous list. For those with a Hct level between 65% to 75%, supportive treatment of fluid boluses of normal saline to prevent the Hct from increasing any further is needed (Kandasamy, 2017).

Partial exchange transfusions were standard treatment for infants that were symptomatic with Hct levels between 60% to 65% or for infants that were asymptomatic with a Hct level greater than 65% due to increased incidence of neurological abnormalities or changes, but are now controversial if they do more harm than good. The AAP still supports partial exchange transfusion for polycythemia but admits that no evidence is available to support that a partial exchange transfusion improves long-term neurological outcomes.

Partial exchange has been to show a dramatic improvement in symptomatic infants, relieving congestive failure and improving CNS function. It also corrects hypoglycemia, relieves respiratory distress and cyanosis, and improves renal function (Kandasamy, 2017).

If a partial exchange transfusion is done, normal saline is the replacement fluid of choice for the removed aliquot of blood. Plasmanate, 5% albumin, or fresh frozen plasma has been used in the past, but due to the advent of stricter precautions for prevention of viral transmission by blood products, use of these items would not seem advisable (Kandasamy, 2017). The formula for calculating the partial replacement of blood volume is: blood volume [patient's Hct − desired Hct] / patient's Hct. The blood volume is the patient's weight × 90 mL/kg of blood.

Collaborative Management of the Infant With Polycythemia. The care of any newborn infant should include a screening Hct determination for polycythemia by 12 hours of age. This allows both detection of polycythemia and adequate observation before symptoms become apparent. Because the initial sample is usually obtained by heel stick or finger stick, detection of a high value should be followed by venipuncture confirmation. The infant should be kept adequately hydrated and closely monitored for hypoglycemia and hypocalcemia. A Hct value over 65% should prompt careful observation of the infant for any symptoms associated with hyperviscosity. If symptoms appear, the infant should undergo partial exchange transfusion. During the partial exchange, the same care should be provided as that given during a single-volume or double-volume exchange transfusion.

COMMON COAGULATION DISORDERS IN THE NEWBORN

Vitamin K Deficiency Bleeding

The liver produces most of the clotting factors, including those of the prothrombin complex. Adequate function of this complex requires the specific action of vitamin K, which is continuously synthesized by bacteria in the bowel. Vitamin K is not directly involved in the synthesis of these factors but is required for the conversion of precursor proteins produced by the liver into active factors having coagulant capabilities. Vitamin K is especially necessary for conversion of prothrombin binding sites into forms that can bind calcium, which is required for the completion of many steps in the clotting cascade.

Vitamin K–dependent factors reach approximately 30% to 70% of adult levels in the cord blood of term infants but quickly drop to half that amount if the infant is not given vitamin K. Because these factors are dependent on gestational age, the more

premature the infant, the lower the levels at birth. The exaggerated drop after birth may be due to poor placental transfer of maternal vitamin K, immature liver function, and delayed synthesis of vitamin K by the bowel. Vitamin K–dependent factors slowly rise but do not reach normal adult levels until approximately 9 months of age. Administration of approximately 0.5 to 1.0 mg of vitamin K can prevent this decline and normalize the prothrombin time (Blackmon et al., 2003).

Hemorrhage during the early neonatal period that can be attributed to a deficiency of vitamin K–dependent factors is classified as vitamin K deficiency bleeding (VKDB) or hemorrhagic disease of the newborn. The incidence is 1/100,000 live births in developed countries in infants who receive vitamin K prophylaxis and 1.7/1,000 for infants who do not receive the prophylaxis at birth, which is 81 times higher incidence (Warren, Miller, Traylor, Sidonio, & Morad, 2013). There are three identified forms of VKDB—early, classic, and later VKDB. The early form, the least common type, is characterized by bleeding within the first 24 hours of life in the scalp, subperiosteal, skin, intracranial, intrathoracic, or intraabdominal sites.

Early bleeding is usually associated with maternal anticonvulsant therapy. It is theorized that anticonvulsants may induce fetal hepatic enzymes involved in the degradation of already low levels of fetal vitamin K. Early neonatal bleeding cannot be prevented by postnatal administration of vitamin K. Daily antenatal administration of large doses of oral vitamin K (10 mg) to mothers receiving anticonvulsant therapy for at least 10 days before delivery was found to be beneficial to the newborn. Vitamin K crosses the placenta, elevating newborn levels of vitamin K for 10 days after birth, with the increase in levels correlating with the timing of the last prenatal dose.

The classic form of VKDB usually occurs during the first 2 to 7 days of life and manifests as generalized and, occasionally, dramatic bleeding. The most common sites are the gastrointestinal tract, umbilicus, circumcision site, skin, and internal organs. Classic VKDB was common in the United States until 1961 when the AAP made the recommendation for the administration of vitamin K to all newborns at birth. The cause of VKDB is now mostly due to parental refusal of the vitamin K shot at birth for multiple reasons. Reasons given by parents in a report by Warren et al. (2013) were: (a) vitamin K is not needed for healthy babies especially if they aren't being circumcised, (b) vitamin K increases the chances of childhood cancer, (c) oral vitamin K supplementation is adequate, (d) breast milk contains more than enough to keep my baby from bleeding, and (e) the baby clotting ability is normal at 8 days of life. All of these reasons are myths and need to be addressed with parents who refuse vitamin K prophylaxis. While breast milk has vitamin K, it is inadequate to make up the deficiency of vitamin K an infant is born with, considering the limited amounts the infant initially takes, if the infant did not receive prophylactic vitamin K. **Emergency Alert: VKDB can be devastating to the newborn infant and is preventable by the provision of a vitamin K injection within 6 hours of birth. It is of utmost importance for the neonatal nurse to dispel any misconceptions regarding vitamin K administration with parents of newborns.**

The late form of VKDB occurs after the first week of life up to 6 to 9 months of age, with the average presentation being between 14 days and 3 months. Late-onset VKDB is more devastating than the early form because of the higher incidence of intracranial hemorrhage (the risk approaches 63%). Permanent neurologic sequelae are seen in 24% of affected infants, and the mortality rate can be as high as 14%. This form of hemorrhagic disease is associated with chronic disease states that interfere with fat absorption or the performance of intestinal flora, as well as parental refusal of vitamin K at birth in breastfed infants. Both early and late hemorrhagic disease of the newborn is intensified in breastfed infants. Definitive diagnosis rests on a history of lack of vitamin K prophylaxis at birth and a prolonged prothrombin time that measures the prothrombin complex clotting factors (Factors II, VII, IX, and X). One test, the protein induced by vitamin K absence or antagonist-II (PIVKA-II) test, is useful in identifying proteins induced by vitamin K deficiency that appear in the plasma of vitamin K–deficient infants. These proteins consist of the inert and functionally defective precursors of prothrombin that are produced when vitamin K levels are deficient.

Several factors can predispose an infant to hemorrhagic disease of the newborn. Almost all these factors involve some form of hepatic dysfunction. The most obvious predisposing factor is the failure of an infant to receive prophylactic vitamin K postnatally. Other risk factors include maternal ingestion of anticonvulsants and coumarin anticoagulants (which interfere with the action of the prothrombin complex factors), birth asphyxia, prolonged labor, and breastfeeding.

Human milk has lower vitamin K content than cow's milk. Infants receiving a commercial formula for 24 hours have prothrombin times similar to those of infants receiving vitamin K after birth. Infants with hepatic dysfunction or bowel malabsorption, although not found strictly in the early neonatal period, can develop vitamin K deficiency despite having received prophylaxis at birth. Such disorders as chronic diarrhea, biliary atresia, hepatitis, cystic fibrosis, and prolonged parenteral nutrition do not allow adequate vitamin K production and can result in low prothrombin complex factors. These infants benefit from weekly vitamin K supplementation (1 mg given intramuscularly), the dose recommended by the AAP Committee on Fetus and Newborn (Blackmon et al., 2003) for postnatal newborn prophylaxis. The suggested preparation for administration to the newborn is the natural aqueous solution of vitamin K rather than the synthetic preparation, which can cause hemolysis. Because of preterm infants' hepatic immaturity and inability to effectively synthesize clotting factors, these infants' response to vitamin K is not as predictable as that of term infants.

Controversy continues over whether intramuscular or oral prophylaxis should be used. At one time, intramuscular administration of vitamin K was linked to the occurrence of childhood cancers; however, this charge has not been substantiated by research. The use of one or two oral doses of vitamin K as an effective treatment is also disputed, and research is needed to determine its efficacy. Research continues in an effort to determine the appropriate timing and number of oral doses of vitamin K and to develop a better oral preparation. Alternative therapies are also being investigated, including antenatal maternal dosing to prevent antenatal intraventricular hemorrhage and postnatal maternal dosing as prophylaxis in the breastfed infant.

Active bleeding caused by VKDB of the newborn consists of parenteral administration of vitamin K in a slow infusion or subcutaneously if unable to obtain venous access. Infants may also require blood replacement or the use of fresh frozen plasma for immediate clotting factor replacement and the use of prothrombin complex concentrates for severe bleeding or intracranial hemorrhage (Diab & Luchtman-Jones, 2015).

Hemophilia

Pathophysiology. Hemophilia A and B are the most common inherited bleeding disorders and are clinically indistinguishable. Classic hemophilia (hemophilia A) is the most frequently inherited coagulation abnormality, accounting for 90% of all genetically

linked coagulopathies and 80% to 85% of all hemophilias, whereas hemophilia B (Christmas disease) occurs in 10% to 15% of cases. Both diseases are X-linked recessive disorders and are passed from mother to son. Hemophilia A is caused by Factor VIII deficiency and hemophilia B is caused by a Factor IX deficiency. Both factors are essential in normal thrombin production. They are needed for the activation of the pathway of Factor X, which converts prothrombin to thrombin. The absence of either factor severely impairs the body's ability to generate both thrombin and fibrin. A hemophiliac's problem is not that of bleeding more rapidly, but of abnormal clot formation. This results in hemorrhage with a potential for significant blood loss. When the clot does form it is often fragile, and rebleeding can occur if proper treatment does not occur.

The severity of the disease is dependent on the baseline level of Factor VIII or Factor IX. Levels of 1% to 2% are associated with severe disease, 2% to 5% with moderate disease, and over 5% with mild disease, a level at which active bleeding rarely occurs. In a retrospective study of hemophiliacs, approximately 44% of a group of severe hemophiliacs were symptomatic during the first week of life, whereas only 14% of a mildly affected group displayed any bleeding during the first 7 days of life (Schulman, 1962).

Diagnosis. Over 50% of hemophiliacs are diagnosed in the neonatal period and have bleeding from a circumcision site, scalp, umbilicus, intramuscular injection site, heel stick site, or brain, with the most common site being a subdural hemorrhage (Diab & Luchtman-Jones, 2015). Not all severe hemophiliacs bleed after circumcision in the early newborn period. The reason for this is unknown, but it has been suggested that tissue thromboplastin release, caused by the circumcision clamp on the foreskin, may initiate the extrinsic pathway and clotting cascade, preventing excessive bleeding. In addition, the use of vacuum or forceps can increase the chance of a hemophiliac bleeding in the brain.

Laboratory tests will be needed to determine if the infant is a hemophiliac. Tests needed will be a partial thromboplastin time, which will be prolonged, both Factor VIII and IX with the affected factor being decreased, and a prothrombin time, a thrombin time, and platelet count which will be relatively normal. Hemophilia A is easier to diagnose in the neonatal period than hemophilia B as Factor IX is reduced at birth and in preterm infants, which can delay diagnosis.

Prenatal diagnosis is possible through amniocentesis or chorionic villus biopsy. Diagnosis involves measurement of the ratio of factor antigen to coagulant antigen in blood samples of fetuses of more than 20 weeks' gestation. If diagnosed with Factor VIII deficiency, the infant should also be evaluated for von Willebrand disease.

Treatment. If diagnosed prenatally, vacuum extraction, forceps, fetal scalp electrodes, and fetal scalp blood sampling should be avoided. There is no consensus on delivery mode, and this should be determined based on maternal and neonatal factors.

Postnatally, the ultimate goal in the treatment of hemophilia is to raise the defective or deficient factor to a level that will prevent significant bleeding. For significant bleeding prior to diagnosis, fresh frozen plasma at 15 to 25 mL/kg should be given, and after diagnosis the specific factor should be given. To have replacement products be as free as possible of transfusion-transmissible diseases, it is recommended that recombinant products be used rather than plasma-derived products. Recombinant Factor VIII concentrates are preferred for hemophilia A, whereas recombinant Factor IX is preferred for hemophilia B (Diab & Luchtman-Jones, 2015; Drelich, 2019; Zaiden, 2017).

Desmopressin (DDAVP, 1-deamino-8-D-arginine vasopressin) is now the treatment of choice for mild to moderate hemophilia A or von Willebrand disease. This medication is not effective in the treatment of hemophilia B. The effectiveness and applicability of this therapy in the newborn are still unknown, but currently it is not recommended if the infant is younger than 3 months of age (Lexicomp Online, 2018).

Von Willebrand Disease

Von Willebrand disease is a disorder of the vWF, which contributes to the adherence of platelets to the endothelium and serves as a carrier protein for Factor VIII. A deficiency in this factor leads to mucocutaneous and postsurgical bleeding, or if it is absent or markedly reduced, it can lead to bleeding in joints and muscles similar to hemophilia A due to the reduction of Factor VIII. vWF levels are high at birth and in the neonatal period; thus, the chance of any bleeding being from von Willebrand disease is low. Since vWF serves as a carrier for Factor VIII, those who do present with bleeding will have signs and symptoms consistent with Factor VIII deficiency.

Infants with von Willebrand disease will present with similar symptoms as hemophiliacs with bleeding into the joints and intracranially. Lab tests to diagnose von Willebrand disease are bleeding time, activated partial thromboplastin time, platelet function screen, blood type, Factor VIII coagulant activity, vWF antigen, vWF activity, and multimetric analysis (Diab & Luchtman-Jones, 2015). Treatment methods are similar to those for hemophilia.

Thrombocytopenia

The normal range of platelets is 150,000 to 450,000/mm^3; the average count in the newborn is approximately 250,000/mm^3. Platelet counts below 150,000/mm^3 are considered abnormal and should be subject to investigation for a possible pathological process. Platelet function in the neonate reaches normal adult levels between the fifth and ninth postnatal days. Although 14% of all preterm infants and 4% of all term infants are thrombocytopenic, with platelet counts below 150,000/mm^3, not all of these infants are ill and will be treated.

Thrombocytopenia is the most common bleeding disorder in the newborn, with 20% to 35% of all NICU admissions and 70% of infants born at less than 1,000 g having the diagnosis during their NICU stay (Sallmon & Sola-Visner, 2012). Of the affected infants, 50% will have platelet counts less than 100,000/mm^3 and 20% will have platelet counts less than 50,000/mm^3 (Cantor, 2015). However, the pathogenesis of the thrombocytopenia can be determined in only 60% of these infants. Abnormalities of the platelet count are due to increased destruction or decreased production, and the underlying cause is mediated by maternal, placental, neonatal, or iatrogenic factors. In most thrombocytopenic newborns, platelet counts are low as a result of increased destruction rather than bone marrow depression. The overall mortality rate for infants with thrombocytopenia is 34%; 22% of these infants exhibit a bleeding diathesis. Infants with a platelet count below 20,000/mm^3 are at particularly high risk for bleeding.

Maternal Factors. Thrombocytopenia is the most common form of hemostatic problem present during pregnancy; 5% to 7% of healthy mothers have platelet counts below 150,000/mm^3. Some of the maternal factors associated with thrombocytopenia are maternal drug ingestion (e.g., chloramphenicol, hydralazine, tolbutamide, and thiazides), maternal eclampsia and hypertension, placental infarction, and immune-mediated maternal platelet antibodies.

Immune-Mediated Maternal Platelet Antibodies

Idiopathic Thrombocytopenia. With immune-mediated thrombocytopenia, in which maternal antibodies destroy platelets, 80% of cases are caused by the autoimmune form, or maternal idiopathic thrombocytopenic purpura (ITP), which strikes women during the second to third decade of life. ITP, now also referred to as autoimmune thrombocytopenia, is a preexisting condition in which maternal lymphocytes produce IgG antiplatelet antibodies (PAIgG) that attack maternal platelets, usually reducing the platelet count to below 150,000/mm^3. These antibodies are specifically directed at platelet antigen and bind to platelets, which are then phagocytized by cells carrying a specific receptor, the Fc receptor. The greatest number of cells with this receptor is found in the reticuloendothelial system of the spleen, which is also the major site of PAIgG production. ITP is often confused with HELLP syndrome, which, in addition to a low platelet count, involves hemolysis and elevated liver enzymes.

Because IgG can cross the placenta, fetal platelets can also be destroyed by the transplacental passage of platelet antibodies, resulting in thrombocytopenia in the fetus and newborn. The mortality rate is 1% to 10% in these affected infants, and the condition can persist postnatally for as long as 4 months.

Neonatal Alloimmune Thrombocytopenia. The remaining 20% of immune-mediated thrombocytopenia are caused by an alloimmune (isoimmune) reaction in which maternal antibodies are produced against foreign fetal platelets (paternally inherited), whereas maternal platelet levels remain normal. This reaction occurs when fetal platelets, which have an antigen not found on maternal platelets, pass into the maternal circulation. The resultant generation of maternal antibodies in response to the fetal platelets is similar to the mechanism behind Rh incompatibility. Unlike Rh incompatibility, alloimmune thrombocytopenia affects 33% to 50% of first pregnancies. The mother develops IgG antibodies that eventually cross into the fetal circulation, resulting in platelet destruction. The PlA1 alloantibodies are responsible for 50% to 80% of neonates with alloimmune thrombocytopenia. This phenomenon occurs in approximately one in 2,000 to one in 5,000 live births. The mortality rate of 10% to 15% in alloimmune thrombocytopenia is higher than that in ITP, because bleeding tends to be more severe. The incidence of intracranial hemorrhage in-utero is reported to be as high as 10% to 15%, with most cases occurring between 30 and 35 weeks' gestation. Treatment consists of transfusion of maternal platelets, exchange transfusion, and use of IVIG. Platelets usually normalize in the newborn by 4 weeks of age.

Antenatal Treatment. The goal of antenatal treatment is to prevent bleeding complications and not severe thrombocytopenia in the newborn. The cornerstone of antenatal treatment is maternal administration of IVIG to the newborn (Winkelhorst, Oepkes, & Lopriore, 2017). IVIG works by (a) diminishing the production of antiplatelet antibodies, (b) interfering with antibody attachment to the surface of the platelets, and (c) reducing platelet destruction by interfering with phagocytic receptors in the reticuloendothelial system. Corticosteroids, specifically prednisone, can be administered with the IVIG. Corticosteroids support the efficacy of IVIG and improve outcomes, but they are not as effective by themselves. Corticosteroids are often given in conjunction with IVIG to reduce the side effect of headaches experienced by mothers who receive IVIG treatment (ACOG Committee on Practice Bulletins—Obstetrics, 2016; Winkelhorst et al., 2017). Pacheo et al. (2011) developed an algorithm based on risk stratification for the administration of IVIG therapy that ACOG bases their 2016 recommendations on. In the algorithm, the administration of steroids and IVIG is based on previous infants with thrombocytopenia with intracranial bleeding (ICH) after 28 weeks' gestation or before 28 weeks' gestation. For mothers who have had no previous infants with ICH, at 20 weeks' gestation, IVIG would be started at 0.5 g/kg/week and prednisone at 0.5 mg/kg/day or IVIG at 2 mg/kg/week. At 32 weeks, IVIG would be given at 2 mg/kg/week and prednisone at 0.5 mg/kg/day. Delivery of the babies is by cesarean section at 37 to 38 weeks' gestation after lung maturity tests are documented. For mothers who have had a previous infant with thrombocytopenia with ICH after 28 weeks' gestation, they would receive 1 g/kg/week of IVIG starting at 12 weeks' gestation, increasing the dose to 2 g/kg/week at 20 weeks or adding prednisone at 0.5 mg/kg/day, and at 28 weeks' gestation given 2 mg/kg/week of IVIG and prednisone at 0.5 mg/kg/day, with delivery by cesarean section at 35 to 36 weeks' gestation after lung maturity tests are documented. Mothers who have had a previous infant with ICH before 28 weeks' gestation should receive IVIG at 2 g/kg/week at 12 weeks' gestation, adding prednisone at 0.5 mg/kg/day at 20 weeks' gestation, and delivering the baby at 35 to 36 weeks' gestation by cesarean section after lung maturity tests are documented. For all three categories, vaginal deliveries are recommended only if percutaneous umbilical cord sampling at 32 weeks shows a platelet count of more than 100,000/mm^3 (Pacheo et al., 2011).

Postnatal Treatment. Postnatal treatment is based on the infant's clinical condition and severity of the thrombocytopenia. Treatment consists of a platelet transfusion as the first line of therapy, IVIG, steroid therapy (prednisone, 1–5 mg/kg/day), or an exchange transfusion with blood less than 2 days old. The major difference in therapy between ITP and alloimmune thrombocytopenia is the use of antigen negative platelets or, if not available, then washed, irradiated, maternal platelets in infants with alloimmune thrombocytopenia.

Neonatal Factors

Neonatal factors associated with thrombocytopenia include asphyxia, an Apgar score of less than 7, DIC, exchange transfusion, infection, smallness for gestational age, necrotizing enterocolitis, hyperbilirubinemia and phototherapy, meconium aspiration, cold injury, polycythemia, pulmonary hypertension, and cardiopulmonary bypass procedure.

Treatment of thrombocytopenia caused by neonatal factors consists initially of amelioration of the underlying problem, followed by symptomatic treatment with platelet transfusion. Transfusion therapy should be considered if platelet counts are in the range of 50,000 to 100,000/mm^3 and active bleeding is present. Platelet transfusion should be considered when the level is below 20,000 to 50,000/mm^3 for stable preterm infants, less than 30,000 to 100,000/mm^3 for unstable preterm infants, and 20,000 to 30,000/mm^3 for term infants even if active bleeding is not present. Transfusion with 10 to 15 mL/kg of platelets will generally yield an increase of 50,000 to 100,000 μL as long as there are no predisposing factors for continued platelet destruction (Diab & Luchtman-Jones, 2015; Pacheo et al., 2011).

Disseminated Intravascular Coagulopathy

DIC is marked by a generalized deficiency of coagulation factors and platelets, which leave the infant predisposed to hemorrhage. Because this condition is triggered by a preexisting illness and does not occur independently, treatment consists of identification and resolution of the underlying problem. Releases of tissue factor and substantial injury to endothelial cells are the two major mechanisms that precipitate DIC (Hall, 2016). The factors most often associated with bleeding that occurs secondary to DIC are

obstetrical complications such as perinatal asphyxia and placental abruption, respiratory distress syndrome, hypoxia, hypotension, necrotizing enterocolitis, and sepsis. Occasionally thrombosis of large vessels can trap platelets and consume an amount of clotting factors sufficient to cause DIC. Mortality rates reach 60% to 80% in infants with DIC who experience severe bleeding (Diab & Luchtman-Jones, 2015).

There is no single laboratory test for DIC, but a combination of tests that help to confirm DIC, which can be difficult to diagnose in the early stages. The best diagnosis is made with taking the clinical picture as well as lab results into consideration. The hematological picture of DIC (Table 13.7) reflects a depletion of platelets, prothrombin, fibrinogen, angiotensin III (AT III), protein C, and Factors V, VIII, and XIII. The prothrombin time and partial thromboplastin time are prolonged and are not corrected by the addition of fresh frozen plasma to the blood sample. The fibrinolytic system is also stimulated, as evidenced by the presence of degradation products of fibrinolysis (i.e., fibrin degradation products or fibrinolytic split products). A commonly used test, measurement of D-dimer, serves as an evaluation of the activation of the fibrinolytic system in that it measures degradation of cross-linked fibrin. However, the D-dimer test may not be very helpful in the newborn because the result is commonly positive in infants who do not have a consumptive coagulopathy (Diab & Luchtman-Jones, 2015).

Successful treatment of DIC depends on alleviation of the underlying cause and maintaining adequate oxygenation and circulation in the neonate. Palliative treatment consists of replacement of deficient clotting factors with fresh frozen plasma and cryoprecipitate, platelet transfusions, and exchange transfusion. Heparin is used infrequently because it carries a higher risk of hemorrhage; it is used only when large-vessel thrombosis occurs (Diab & Luchtman-Jones, 2015).

Protein C and S Deficiency. Protein C and S are two of several anticoagulant proteins and are inherited in an autosomal dominant pattern. Heterozygous deficiency causes increased incidence of thrombosis, but is rare in the neonatal period. Homozygous protein C or S deficiency will present in the neonatal period and can occur in the first few hours to days of life. Patients affected by a protein C or S deficiency will present with purpura fulminans, severe DIC, and life-threatening thrombosis. Diagnosis is done with laboratory tests that are consistent with DIC, and there is no measurable protein by assay. Treatment, if done early, can improve clinical outcomes. Treatment consists of the administration of fresh frozen plasma. A protein C concentrate is available in the United States for compassionate use only. Patients with this disease will need to be on lifelong warfarin therapy (Diab & Luchtman-Jones, 2015).

TABLE 13.7

LABORATORY FINDINGS IN DISSEMINATED INTRAVASCULAR COAGULATION

Laboratory Test	Results
Platelet count	Decreased
Prothrombin time	Prolonged
Partial thromboplastin time	Prolonged
Fibrinogen	Decreased
Factor V and VIII	Decreased
Factor VII and IX	Normal
Angiotensin III	Decreased
Protein C	Decreased
Heparin cofactor II	Decreased
Fibrin	Elevated
Fibrinogen degradation products	Elevated
D-dimer	Increased
Hematocrit	Decreased
Bleeding time	Prolonged
Red blood cell on smear	Fragmented

Source: Information from Diab, Y., & Luchtman-Jones, L. (2015). Hematologic and oncologic problems in the fetus and neonate. In R. J. Martin, A. A. Fanaroff, & M. C. Walsh (Eds.), *Fanaroff and Martin's neonatal-perinatal medicine: Diseases of the fetus and infant* (10th ed., pp. 1294–1343). Philadelphia, PA: Elsevier.

Differential Diagnosis of Newborn Coagulopathies

Analysis of a number of factors can often aid in the identification of the specific coagulopathy affecting an infant. Careful evaluation of the following factors can pinpoint the correct diagnosis and influence the choice of therapy or intervention:

- A familial history of a bleeding disorder, such as hemophilia
- A maternal history of a bleeding disorder, as in autoimmune thrombocytopenia
- An obstetrical history that suggests a possible abnormality, as in maternal alloimmunization or hypofibrinogenemia
- An adverse neonatal history, such as with hypoxia or asphyxia
- Failure to administer prophylactic vitamin K at birth
- Physical manifestations of a bleeding disorder (e.g., obvious bleeding, the presence or absence of petechiae or ecchymosis) and the infant's overall condition
- Laboratory data that identify specific abnormalities, such as specific coagulation factor deficiencies, thrombocytopenia, and prolonged prothrombin time, partial thromboplastin time, and clotting times

Collaborative Management of a Coagulopathy

Care of an infant with a bleeding diathesis should be aimed at prevention of further injury or bleeding. Supportive care of fragile tissue and limiting the number of blood draws from sites other than central catheters are of great importance in the infant who lacks adequate clotting factors to control bleeding. Appropriate administration of platelets, clotting factors, or blood products requires the correct equipment, the correct method of administration, and conscientious monitoring of vital signs to ensure effective

therapy without causing further harm to the infant. Wise decisions regarding replacement blood products are now important in light of the severe and potentially lethal sequelae of acquired infection. Adopting guidelines for transfusion therapy may safeguard infants and eliminate unnecessary exposure to blood products (see Transfusion Guidelines for Newborns). Monitoring of laboratory tests to determine continuing needs and the efficacy of therapy is important throughout the infant's course of therapy.

When blood or blood products are administered, the infant must be evaluated continuously for signs of fluid overload and untoward reaction. Although blood reactions are rare in the newborn, they tend to occur within the first 15 minutes of blood or blood product administration. Signs of such reactions include rashes, tachycardia, hypertension, hematuria, cyanosis, and hyperthermia. Throughout the acute course of illness, the Hct values and the state of perfusion, rather than the percentage of the infant's blood volume removed, should govern the decision on whether to transfuse. Symptoms of hypovolemia include metabolic acidosis, hypotension, poor perfusion, tachycardia, cyanosis, and shock (Diab & Luchtman-Jones, 2015).

SUPPORT OF THE FAMILY OF THE INFANT WITH HEMATOLOGIC DISORDER

An ill neonate is a crisis for families as no one expects their baby to be born prematurely or ill. When a diagnosis of a hematologic disorder occurs, the physician should discuss with the parents the disease, cause, treatment, and outcomes. Parents have a role in deciding the goals of the care to be delivered to their baby, but they cannot make an informed decision unless they have been presented complete and reliable information. Unfortunately, many times this type of information may not be available until after the acute phase of the disease.

During care of the infant with a hematologic disorder, healthcare professionals should keep the parents informed of what is occurring with their newborn and parents' wishes should be honored, if appropriate. More discussion of the care of the family is discussed in the chapters in Unit VI.

BLOOD COMPONENT REPLACEMENT THERAPY

Whole Blood

This product is not used for routine volume expansion because of the Hct dilution that occurs. It is used in surgical procedures that require large volumes of blood for replacement, for exchange transfusions, and for priming heart-lung oxygenators for extracorporeal membrane oxygenation (Fasano et al., 2015).

Packed Red Blood Cells

Blood is "hard spun" to concentrate cells (Hct 70–90) and to allow the supernatant to be removed. Because of this form of preparation, less volume can be administered. Packed RBCs can be reconstituted with normal saline, 5% albumin, or fresh frozen plasma. Packed RBCs can be used in exchange transfusions or in the treatment of anemia in the acutely ill or symptomatic convalescent infant (Fasano et al., 2015; Patel & Josephson, 2018).

Washed Red Blood Cells

For additional protection, RBCs can be washed to remove as much of the plasma, nonviable RBCs, WBCs, and metabolic wastes, especially potassium, as possible. After washing, washed RBCs contain 10% to 20% fewer RBCs and 99% of plasma proteins and 85% of WBCs are removed (Keir, Wilkinson, Andersen, & Stark, 2016).

Frozen Deglycerolized Red Cells

Frozen storage of deglycerolized RBCs allows preservation of rare units of blood, but the cost of preparation increases considerably. In addition, this product tends to have a higher potassium content and hemoglobin concentration. Centrifuging it, removing the supernatant, and diluting it to the desired Hct level tend to control these problems (Lagerberg, 2015).

Fresh Frozen Plasma

Fresh frozen plasma provides a rich source of coagulation factors to treat acquired coagulation factor deficiencies; 10 to 15 mL/kg, which contains 1 IU/mL of all clotting factors, raises the overall level of clotting factor activity by 20% to 30%. Fresh frozen plasma can often normalize prolonged prothrombin and partial thromboplastin times in the newborn who has a generalized deficiency in quantity and activity of available clotting factors (Fasano et al., 2015; Patel & Josephson, 2018).

Platelets

Platelet transfusions are administered either therapeutically or prophylactically to prevent or decrease the risk of hemorrhage induced by thrombocytopenia or other platelet abnormalities. In stable infants, a platelet count of less than 30,000/μL will result in a transfusion of platelets, and a count of less than 50,000/μL in clinically unstable infants will prompt consideration of a transfusion. The infusion of 10 to 15 mL/kg of platelets should result in an increase in the platelet count of 50,000 to 100,000/μL. An important caveat: Platelets require a special administration set for proper infusion (Fasano et al., 2015; Patel & Josephson, 2018).

Granulocytes

Granulocytes, which are used for infusion in septic infants with severe neutropenia, are prepared from fresh donor blood through the process of plasmapheresis. WBCs are removed from the unit of blood, but a large number of RBCs remain. For this reason, the donor unit must be typed and cross-matched to the infant for blood type and Rh compatibility. WBCs are usually irradiated to eliminate donor T cells in an effort to prevent graft-versus-host responses. Granulocytes are infused at 10 to 15 mL/kg. They are given on a daily basis until the infant's clinical status and neutrophil count improve. Infants must be monitored for signs of pulmonary reactions and febrile transfusion reactions. The efficacy of granulocyte transfusions remains controversial (Fasano et al., 2015).

Cryoprecipitate

This form of plasma preparation is rich in Factors VIII and XIII and fibrinogen and is useful in the treatment of hemophilia. Because it is a single-donor collection, the risk for infection is lower than with pooled substances. Each bag of cryoprecipitate transfused raises fibrinogen levels by 100 mg/dL (Fasano et al., 2015; Patel & Josephson, 2018).

Factor Concentrates

Factor concentrates are used as specific therapy for identified factor deficiencies. Factor concentrates are available commercially and are an option for treatment after consultation with hematology. It is important to remember that infants often do not require treatment during the neonatal period as they may not exhibit signs of bleeding (Saxonhouse, 2018).

Protocols

Management of Jaundice in the Newborn Nursery. Knowing which neonate will or will not develop sequelae as a result of hyperbilirubinemia is the challenge that healthcare professionals must face when caring for the newborn. The neonatal nurse is a key player in recognizing the onset of hyperbilirubinemia and in notifying the practitioner.

A major factor that makes a newborn more prone to developing more severe jaundice is prematurity. The more premature a baby is, the greater the risk. One of the several reasons for this is that the premature infant liver has a delay in reaching maximum concentrations of uridine diphospho-glucuronosyltransferase (UGT), the substance that helps with the breakdown of bilirubin. The premature baby may feed less than a term baby, which leads to fewer bowel movements, another essential component in eliminating bilirubin from the body (Kaplan et al., 2015). The late preterm infants are especially at risk, as they often do not appear ill and are hence referred to as the "great pretenders," pretending to be healthy newborns.

As stated earlier in this chapter, the sequelae related to hyperbilirubinemia is acute bilirubin encephalopathy (transient mild encephalopathy) and chronic bilirubin encephalopathy (kernicterus) (Kaplan et al., 2015). Kernicterus is a preventable disease if a newborn's jaundice is recognized and managed properly. The AAP in 1994 developed guidelines for healthcare professionals to manage hyperbilirubinemia in the newborn, revised them in 2004, clarified them in 2009, and at the writing of this chapter the AAP was revising the guidelines. A study by Burke et al. (2009) showed that since the implementation of the AAP 1994 guidelines the incidence of hospitalizations with a diagnosis of kernicterus in the United States has decreased, showing that proper adherence to the AAP guidelines helps to prevent long-term sequelae of hyperbilirubinemia.

Transfusion Guidelines for Newborns

As discussed earlier in this chapter, there are risks associated with transfusions and because of that there are now more restrictive guidelines for when to transfuse an infant. The following are current recommendations based on evidence.

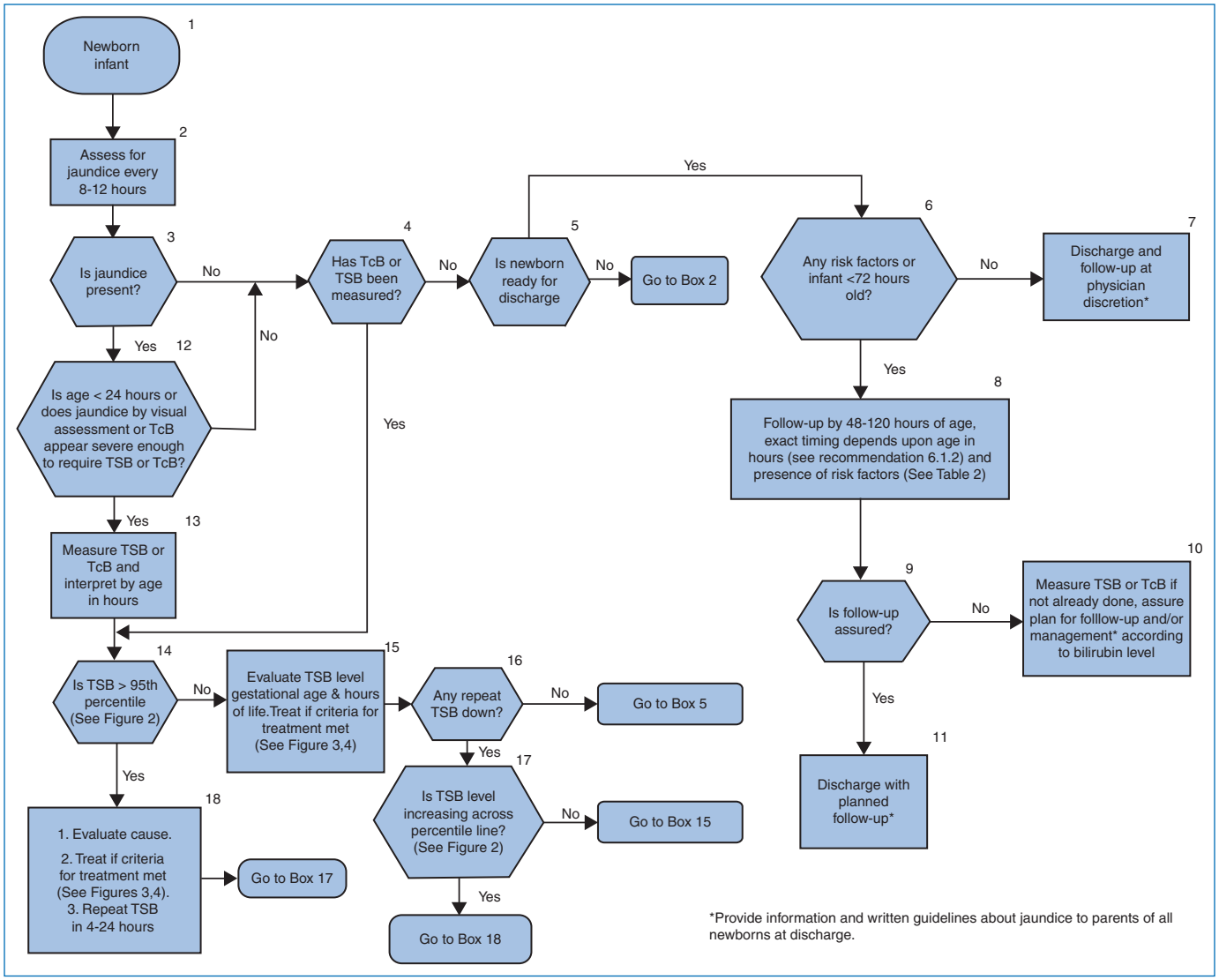


FIGURE 13.13 Algorithm for the management of jaundice in the newborn nursery.

TcB, transcutaneous bilirubin; TSB, total serum bilirubin.

Source: Maisels, M. J., Baltz, R. D., Bhutani, V. K., Newman, T. B., Palmer, H., Rosenfeld, W., . . . Weinblatt, H. B. (2004). Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics, 114,* 297–316. doi:10.1542/peds.114.1.297

General Principles of Transfusion

1. For both term and preterm infants, the need for transfusion is based on the infants' need for increased oxygen to the tissue as evidenced by the clinical picture of the infant.
2. Measurement of the Hgb and Hct values should be obtained from the central circulation when determining the need for a transfusion. If unable to obtain a central Hgb and Hct, a heel stick may be obtained after warming the heel for 3 to 5 minutes.
3. The recommended volume of transfusion is 20 mL/kg for term and preterm infants needing transfusion, unless their Hct level is greater than 29%, in which case they would get 10 mL/kg. If infant is small with a Hct level greater than 29%, then it can be used if significant blood loss from phlebotomy is anticipated.
4. If the infant has received HuEPO, then the reticulocyte count, the postnatal day of age, the need for additional oxygen, and the overall status of the infant need to be considered in addition to the Hgb and Hct values.
5. Leukocyte-reduced and irradiated PRBC should be used for all neonatal transfusions to prevent transfusion reactions in the neonate.
6. CMV-negative PRBC should be used for neonates, but especially for immunodeficient neonates, those awaiting transplants, or premature neonates of CMV-negative mothers to prevent CMV transmission.
7. Blood should be given over 2 to 4 hours, unless hemodynamically unstable or with hypovolemia due to blood loss, in which case it should be given over 1 to 2 hours.
8. Fetuses and neonates with a hemolytic disease that need an exchange transfusion or transfusion have to have blood that is compatible with their blood.
9. O-negative whole blood should only be used as a last resort in neonates, as it contains antibodies against A and B blood groups and leukocytes.

Transfusion for Acute Blood Loss. For acute blood loss, immediate fluid resuscitation with 0.9% normal saline at 10 mL/kg should be given while obtaining the blood.

Blood transfusions should be given to infants who have:

1. Acute blood volume loss greater than 20%
2. Acute blood volume loss greater than or equal to 10% with signs of decreased oxygen delivery
3. An ongoing hemorrhage

Transfusion for Chronic Blood Loss. Blood transfusions for infants with chronic blood loss is based on Hgb and Hct levels, the need for oxygen/respiratory support, and age.

SUMMARY

This chapter outlines the common hematologic neonatal problems and evidence-based interventions. The nurse's role is crucial to improve outcomes. Anticipation of problems, very thorough assessment, and ongoing evaluation of treatment response are key to providing the best possible care.

CASE STUDY

■ **Identification of Problem.** A 4-day-old infant is admitted to the NICU with a history of jaundice and lethargy from his local pediatrician's office. A TSB test drawn at the pediatrician's office had a result of 38 mg/dL.

■ **Assessment: History and Physical.** The baby boy was born at 37 weeks' gestation at 3.2 kg to a 28-year-old, gravida 2, para 1, AB 1 mother of Asian descent. The pregnancy was complicated by a positive Group B bacterial streptococcal culture, and the mother was treated with prophylactic antibiotics prior to delivery. The baby was born by vacuum-assisted vaginal delivery. The baby was vigorous at birth with Apgar scores of 8 and 9. The mother's blood type was O positive and the baby's blood type was A positive. The Coombs test was positive. The breastfed infant had an unremarkable course at the delivery hospital but was noted to be jaundiced at 32 hours of age. A TSB was done with a result of 12.8 mg/dL. He was discharged home at 46 hours of age.

On admission to the NICU, the infant was noted to be severely jaundiced but pink. His vital signs were within normal limits with an axillary temperature of 98.5°F, heart rate of 150 beats/min, respiratory rate of 55 breaths/minute, and blood pressure of 60/36 mmHg with a mean of 48 mmHg. His weight on admission was noted to be 2.72 kg, a 15% loss. His examination was nonremarkable, except for his decreased response to stimuli, poor muscle tone, poor suck, and a decreased Moro. His glucose screen was 50.

■ **Differential Diagnosis.** Many conditions are known to cause jaundice and lethargy in the newborn. The most common are hyperbilirubinemia, ABO incompatibility, G6PD, hypothyroidism, dehydration secondary to inadequate breastfeeding, sepsis, and kernicterus.

■ **Diagnostic Tests.** To determine the cause of the jaundice and lethargy, a CBC with differential, repeat TSB, electrolytes, calcium, glucose, and liver function tests, as well as T4/thyroid-stimulating hormone (TSH), G6PD screen, a hemoglobin electrophoresis, and blood culture all need to be ordered.

■ **Working Diagnosis.** The baby's repeat bilirubin was 40 mg/dL; his CBC showed a WBC of 12.2/mm^3, with 35% segs, and 4% bands; his hemoglobin was 10.0 g%; his Hct was 28%, and his reticulocyte count was 3%. The G6PD screen was adequate. Electrolytes, liver function tests, calcium, and glucose were all within normal limits, and the free T4 was 1.1 ng/dL (NL: 0.9–2.1), but TSH was 25.76 mIU (NL: 1.7–9.1). The hemoglobin electrophoresis was "A, F." These test results suggest a working diagnosis of hyperbilirubinemia secondary to ABO incompatibility and hypothyroidism.

■ **Development of Management Plan.** The main goal for an infant with a bilirubin of 40 mg/dL is to reduce the bilirubin level as quickly as possible to prevent kernicterus. While the blood is being typed and cross-matched, the infant needs to be placed in a neutral thermal environment, made NPO, have a peripheral IV placed and IV fluids of D10.2NS with 20 KCl/L at 120 mL/kg/hour, and started on antibiotics. An attempt should be made to do a cutdown of the umbilical cord to place an umbilical vein and arterial catheter for the exchange transfusion. Double phototherapy lights need to be started immediately.

■ **Implementation and Evaluation of Effectiveness.** A double-volume exchange transfusion was done over 3 hours. The infant received calcium and glucose boluses during the transfusion for low calcium and glucose. Phototherapy lights were continued after the transfusion. His laboratory tests of TSB, electrolytes, CBC with differential, glucose, and calcium were repeated after the exchange transfusion was completed. His postprocedure TSB level was 23 mg/dL.

During the exchange transfusion the baby became apneic, which required intubation and the need for ventilation for 1 day. He received antibiotics for 2 days and phototherapy for 4 days. He was started on Synthroid for his abnormal TSH.

On day of life 10, the TSB was 10 mg/dL. On examination, the infant was slightly hypertonic. A BAER was normal, but an MRI was consistent with kernicterus. He was discharged home with a referral made to the neonatal developmental clinic and early intervention to follow his developmental status.

EVIDENCE-BASED PRACTICE BOX

Anemia of prematurity is a common occurrence in premature infants due to factors discussed earlier in this chapter. The treatment mainstay for this condition has been transfusion with PRBCs, but in the past decade there have been decreasing numbers of blood transfusions given to ill and premature neonates for reasons discussed earlier in this chapter. The decreased incidence of using PRBCs is related to several studies as well as the use of HuEPO.

Bell et al. (2005) published their randomized clinical trial that compared a restrictive versus liberal transfusion guideline. The goal of the trial was to determine if restrictive transfusion guidelines in premature infants decreased the number of transfusions and number of donor exposures without increasing adverse outcomes. The study enrolled 100 premature neonates between 500 and 1,300 g that were assigned to one of the two groups with similar gestational ages and birth weights. The results showed that the liberal group had more transfusions, though not more donor exposures. The infants in the restrictive transfusion group were more likely to have an intraparenchymal brain hemorrhage or periventricular leukomalacia as well as having more apnea and bradycardic episodes.

A large multi-center randomized controlled trial study called the Premature Infant in Need of Transfusion (PINT; Kirpalani et al., 2006) looked at the effect of transfusions in premature babies less than 1,000 g and the primary outcome of death before discharge. Secondary outcomes were incidences of retinopathy of prematurity, bronchopulmonary dysplasia, or abnormal brain ultrasound at discharge. The infants were assigned to either a restrictive or liberal blood transfusion algorithm based on Hct within 48 hours of birth. The trial had over 400 infants and the two groups had similar numbers with infants of similar weights and gestational ages. Results of the study demonstrated that the restrictive transfusion group had less transfusions, but there was no statistical difference in the primary or secondary outcomes.

In 2011, Fredrickson et al. published a small clinical trial of 41 infants with birth weights between 500 and 1,300 g at birth. The trial examined effects of a low or high Hct threshold for transfusion on oxygen transport, lactic acid, oxygen consumption, and cardiac output. The study results showed that while both groups had an increase in systemic oxygen transport and a decrease in lactic acid following a transfusion, neither group had a significant change in oxygen consumption as a result of a transfusion. The only difference noted was that the low Hct group did have a decrease in cardiac output after the transfusion, implying that the neonates had increased their cardiac output to increase oxygenation due to anemia. The results from this study, though the numbers were small, showed that neonates with low Hct could benefit from transfusions.

Study results vary, though it appears that the restrictive transfusion guideline has the advantage of less exposure to blood with no more significant adverse outcomes. Clinical trials need to continue on this subject in the neonatal period as well as look at the long-term neurodevelopmental outcomes as the children get older.

References

Bell, E. F., Strauss, R. G., Widness, J. A., Mahone, L. T., Mock, D. M., Seward, V. J., . . . Zimmerman, M.B. (2005). Randomized trial of liberal versus restrictive guidelines for red blood cell transfusion in preterm infants. *Pediatrics, 115*(6), 1685–1691. doi:10.1542/peds.2004-1884

Fredrickson, L. K., Bell, E. F., Cress, E. J., Johnson, K. J., Zimmerman, M. B, Mahoney, L. T., . . . & Strauss, R. G. (2011). Acute physiological effects of packed red blood cell transfusion in preterm infants with different degrees of anemia. *Archives of Diseases in Childhood—Fetal and Neonatal Edition, 96*(4), f249–f253. doi:10.1136/adc.2010.191023

Kirpalani, H., Whyte, R. K., Anderson, C., Asztalos, E. V., Heddle, N,. Blajchman, M. A., . . . PINT Investigators. (2006). The premature infant in need of transfusion (PINT) study: A randomized controlled trial study of a restrictive (low) versus liberal (high) transfusion threshold for extremely low birth weight infants. *Journal of Pediatrics, 149*(3), 301–307. doi:10.1016/j.jpeds.2006.05.011

ONLINE RESOURCES

Cochrane Library. Retrieved from http://www.cochranelibrary.com

Cochrane Reviews. Retrieved from https://www.cochrane.org/search/site/cochrane%20reviews?f%5B0%5D=im_field_terms_cochrane_library%3A51052

Emedicine. Retrieved from http://www.emedicine.medscape.com

MedlinePlus. Retrieved from http://www.nlm.nih.gov/medlineplus

National Blood Clot Alliance. Retrieved from http://www.stoptheclot.org

National Hemophilia Organization. Retrieved from http://www.hemophilia.org

Neonatology on the Web. Retrieved from http://www.neonatology.org

REFERENCES

Aher, S. M., & Ohlsson, A. (2012). Early vs late erythropoietin for preventing red blood cell transfusion in preterm and or low birth weight infants. *Cochrane Database of Systematic Reviews*, (10), CDC004865. doi:10.1002/14651858.CD004865.pub3

Al-Wassia, H., & Shah, P. S. (2015). Efficacy and safety of umbilical cord milking at birth: A systematic review and meta-analysis. *JAMA Pediatrics, 169*(1), 18–25. doi:10.1001/jamapediatrics.2014.1906

American Academy of Pediatrics. (2017). Statement of endorsement: Delayed cord clamping after birth. *Pediatrics, 139*(6), e20170957. doi:10.1542/peds.2017-0957

American Academy of Pediatrics Subcommittee on Hyperbilirubinemia (2004). Management of hyperbilirubinemia in the newborn infant 35 or more weeks gestation. *Pediatrics, 114*(1); 297-316. doi: 10.1542/peds.114.1.297

American Academy of Pediatrics & the American College of Obstetrics and Gynecology. (2017). *Guidelines for perinatal care* (8th ed.). Elk Grove, IL: Author.

American College of Obstetricians and Gynecologists' Committee on Obstetric Practice. (2017). Committee opinion no. 684: Delayed umbilical cord clamping after birth. *Obstetrics and Gynecology, 129*(1), e5–e10. doi:10.1097/AOG.0000000000001860

American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. (2016). Practice bulletin no. 166: Thrombocytopenia in pregnancy. *Obstetrics and Gynecology, 128*(3), e43–e53. doi:10.1097/AOG.0000000000001641

American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. (2017). Practice bulletin no. 181: Prevention of Rh D alloimmunization. *Obstetrics and Gynecology, 130*(2), e57–e70. doi:10.1097/AOG.0000000000002232

Andrew, M., Paes, B., & Johnston, M. (1990). Development of the hemostatic system in the neonate and young infant. *American Journal of Pediatric Hematology/Oncology, 12*, 97–98. doi:10.1097/00043426-199021000-00019

Antoniani, C., Romano, O., & Miccio, A. (2017). Concise review: Epigenetic regulation of hematopoiesis: Biological insights and therapeutic applications. *Stem Cells Translational Medicine, 6*(12), 2106–2114. doi:10.1002/sctm.17-0192

Baker, R. D., Greer, F. A., & The Committee on Nutrition. (2010). Diagnosis and prevention of iron deficiency and iron deficiency anemia in infants and young children (0-3 years age). *Pediatrics, 126* (5), 1040–1050. doi:10.1542/peds.2010-2576

Bhutani, V. K., & Lamola, A. A. (2017). Mechanistic aspects of phototherapy for neonatal hyperbilirubinemia. In R. A. Polin, S. H. Abman, D. H. Rowitch, W. E. Benitz, & W. W. Fox (Eds.), *Fetal and neonatal physiology* (5th ed., pp. 942–952). Philadelphia, PA: Elsevier. doi:10.1016/B978-0-323-35214-7.00098-6

Bhutani, V. K., Papile, L.-A., Baley, J. E., Carlo, W. A., Cummngs, J. J., Kumar, P., . . . Watterberg, K. L. (2011). Phototherapy to prevent severe neonatal hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics, 128*, e1046–e1052. doi:10.1542/peds.2011-1494

Bhutani, V. K., Poland, R., Meloy, L. D., Hegyi, T., Fanaroff, A. A., & Maisels, M. J. (2016). Clinical trial of tin mesoporphyrin to prevent neonatal hyperbilirubinemia. *Journal of Perinatology, 36*, 533–539. doi:10.1038/jp.2016.22

Bhutaini, V. K., Wong, R. J., & Stevenson, D. K. (2016). Hyperbilirubinemia in preterm neonates. *Clinics in Perinatology, 43*, 215–232. doi:10.1016/j.clp.2016.01.001

Blackburn, S. T. (2017). *Maternal, fetal, & neonatal physiology* (5th ed.). Maryland Heights, MO: Elsevier.

Blackmon, L., Batton, D. G., Bell, E. F., Engle, W. A., Kanto, W. P., Jr., Martin, G. I., . . . Stark, A. R. (2003). Controversies concerning vitamin K and the newborn. *Pediatrics, 112*(1), 191–192. doi:10.1542/peds.112.1.191. (Reaffirmed 2006, 2009, 2015)

Brown, M. (1988). Physiologic anemia of infancy: Normal red cell values and physiology of neonatal erythropoiesis. In J. Stockman & C. Pochedly (Eds.), *Developmental and neonatal hematology*. (pp. 249–274). New York, NY: Raven Press.

Burke, B. L., Robbins, J. M., Bird, T. M., Hobbs, C. A., Nesmith, C., & Tifford, J. M. (2009). Trends in hospitalizations for neonatal jaundice and kernicterus in the United States, 1988–2005. *Pediatrics, 123*(2), 524–532. doi:10.1542/peds.2007-2915

Cantor, A. B. (2015). Hemostasis in the newborn and infant. In S. H. Orkin, D. E. Fisher, D. Ginsburg, A. T. Look, S. E. Lux, & D. Nathan (Eds.), *Nathan and Oski's hematology and oncology of infancy and childhood* (8th ed., pp. 128–158). Philadelphia, PA: Elsevier.

Cassady, G. (2016). Anemia of prematurity. In T. Rosenkrantz (Ed.) *Medscape*. Retrieved from https://emedicine.medscape.com/article/978238

Castro, L. C., & Hobel, C. J. (2016). Rhesus alloimmunization. In N. F. Hacker, J. C. Gambone, & C. J. Hobel (Eds.), *Hacker & Moore's essentials of obstetrics and gynecology* (6th ed., pp. 194–200). Philadelphia, PA: Elsevier.

Christensen, R. (1989). Recombinant erythropoietic growth factors as an alternative to erythrocyte transfusion for patients with "anemia of prematurity." *Pediatrics, 83*(5), 793–796. Retrieved from https://pediatrics.aappublications.org/content/83/5/793

Christensen, R. D., Lambert, D. K., Henry, E., Eggert, L. D., Yaish, H. M., Reading, N. S., & Prchal, J. T. (2012). Unexplained extreme hyperbilirubinemia among neonates in a multihospital healthcare system. *Blood Cells, Molecules and Diseases, 50*, 105–109. doi:10.1016/j.bcmd.2012.10.004

Costa, K. (2018). Hematology. In *The Harriet Lane handbook* (pp. 364–394). Philadelphia, PA: Elsevier.

Deshpande, P. G., & Wagle, S. (2017). Breast milk jaundice. In M. Aslam (Ed.), *Medscapse.* Retrieved from http://emedicine.medscape.com/article/973629

Diab, Y., & Luchtman-Jones, L. (2015). Hematologic and oncologic problems in the fetus and neonate. In R. J. Martin, A. A. Fanaroff, & M. C. Walsh (Eds.), *Fanaroff and Martin's neonatal-perinatal medicine: Diseases of the fetus and infant* (10th ed., pp. 1294–1343). Philadelphia, PA: Elsevier.

Downs, E., & Gourley, G. R. (2015). Neonatal jaundice and disorders of bilirubin metabolism. In S. H. Orkin, D. E. Fisher, D. Ginsburg, A. T. Look, & S. E. Lux (Eds.), *Nathan and Oski's hematology and oncology of infancy and childhood* (8th ed., pp. 101–127). Philadelphia, PA: Saunders/Elsevier.

Drelich, D. A. (2019). Hemophilia A. In S. Nagalla (Ed.), *Medscape*. Retrieved from https://emedicine.medscape.com/article/779322

Elimian, A., Goodman, J., Escobedo, M., Nightingale, L., Knudston, E., & Williams, M. (2014). Immediate compared with delayed cord clamping in preterm neonate: A randomized control trial. *Obstetrics and Gynecology, 124*(6), 1075–1079. doi:10.1097/AOG.0000000000000556

Fasano, R., Said, M., & Luban, N. (2015). Blood component therapy for the neonate. In R. Martin, A. Fanaroff, & M. Walsh (Eds.), *Neonatal-perinatal medicine. Diseases of the fetus and newborn* (10th ed., pp. 1344–1361). Philadelphia, PA: Elsevier.

Flaherman, V. J., Maisels, J., Brodribb, W., Noble, L., Brent, N., Bunik, M., ... Young, M. (2017). ABM clinical protocol #22: Guidelines for the management of jaundice in the breastfeeding infant 35 weeks or more of gestation—Revised 2017. *Breastfeeding Medicine, 12*, 250–257. doi:10.1089/bfm.2017.29042.vjf

Fyfe, T. M., Ritchey, M. J., Taruc, C., Crompton, D., Galliford, B., & Perrin, R. (2014). Appropriate provision of anti-D prophylaxis to RhD negative pregnant women: A scoping review. *BMC Pregnancy and Childbirth, 14*, 411. doi:10.1186/s12884-014-0411-1

Gallagher, P. G. (2015). The neonatal erythrocyte and its disorders. In S. H. Orkin, D. G. Nathan, D. Ginsburg, A. T. Look, D. E. Fisher, & S. E. Lux (Eds.), *Nathan and Oski's hematology and oncology of infancy and childhood* (8th ed., pp. 52–75). Philadelphia, PA: Elsevier.

Hall, J. E. (2016). *Guyton and Hall textbook of medical physiology* (13th ed.). Philadelphia, PA: Elsevier.

Hulzebos, C. V., & Dijk, P. H. (2014). Bilirubin-albumin binding, bilirubin/albumin ratios, and free bilirubin levels: Where do we stand? *Seminars in Perinatology, 38*, 412–421. doi:10.1053/j.semperi.2014.08.004

Kandasamy, J. (2017). Polycythemia of the newborn. In T. Rosenkrantz (Ed.), *Medscape*. Retrieved from https://emedicine.medscape.com/article/976319

Kaplan, M., Bromiker, R., & Hammerman, C. (2011). Severe hyperbilirubinemia and kernicterus: Are these still problems in the third millennium? *Neonatology, 100*, 354–362. doi:10.1159/000330055

Kaplan, M., Wong, R. J., Sibley, E., & Stevenson, D. K. (2015). Neonatal jaundice and liver disease. In R. Martin, A. Fanaroff, & M. Walsh (Eds.), *Neonatal-perinatal medicine. Diseases of the fetus and newborn* (10th ed., pp. 1618–1673). Philadelphia, PA: Elsevier.

Keir, A. K., Wilkinson, D., Andersen, C., & Stark, M. J. (2016). Washed versus unwashed red blood cells for transfusion for the prevention of morbidity and mortality in preterm infants. *Cochrane Database of Systematic Reviews*, (1), CD011484. doi:10.1002/14651858.CD011484.pub2

Lagerberg, J. W. (2015). Cryopreservation of red blood cells. *Methods in Molecular Biology, 1257*, 353–367. doi:10.1007/978-1-4939-2193-5_17

Lexicomp Online. (2018). *Lexi-Drugs online*. Hudson, OH: Author.

Liley, H. G., Gardner, G., Lopriore, E., & Smits-Wintjens,V. (2015). Immune hemolytic disease. In S. H. Orkin, D. E. Fisher, D. Ginsburg, A. T. Look, D. E. Fisher, & S. E. Lux (Eds.), *Nathan and Oski's hematology and oncology of infancy and childhood* (8th ed., pp. 76–100). Philadelphia, PA: Elsevier.

Maisels, M. J. (2015). Managing the jaundiced newborn: A persistent challenge. *Canadian Medical Association Journal, 187*, 335–343. doi:10.1503/cmaj.122117

Maisels, M. J., Baltz, R. D., Bhutani, V. K., Newman, T. B., Palmer, H., Rosenfeld, W., . . . Weinblatt, H. B. (2004). Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics, 114*, 297–316. doi:10.1542/peds.114.1.297

Maisels, M. J., Bhutani, V. K., Bogen, D., Newman, T. B., Stark, A. R., & Watchko, J. F. (2009). Hyperbilirubinemia in the newborn infant ≥ 35 weeks' gestation: An update with clarifications. *Pediatrics, 124*, 1193–1198. doi:10.1542/peds.2009-0329

Meleti, D., De Oliveira, L. G., Araujo Júnior, E., Caetano, A. C., Boute, T., Nardozza, L. M., & Moron, A. F. (2013). Evaluation of passage of fetal erythrocytes into maternal circulation after invasive obstetric procedures. *Journal of Obstetrics and Gynaecology Research, 39*, 1374–1382. doi:10.1111/jog.12073

Mintz, P. D. (2010). Rh immune globulin. In P. D. Mintz (Ed.), *Transfusion therapy: Clinical principles and practice* (3rd ed, pp. 493–510). Bethesda, MD: AABB Press.

Morioka, I., Iwatani, S., Koda, T., Iijima, K., & Nakamura, H. (2015). Disorders of bilirubin binding to albumin and bilirubin-induced neurologic dysfunction. *Seminars in Fetal & Neonatal Medicine, 20*, 31–36. doi:10.1016/j.siny.2014.11.001

Nunes dos Santos, A. M., & Trindade, C. E. P. (2011). Red blood cell transfusions in the neonate. *NeoReviews, 12*, e13. doi:10.1542/neo.12-1-e13

Ohls, R. K. (2015). Anemia. In R. Polin & M. Yoder (Eds.), *Workbook in practical neonatology* (5th ed., pp. 107–136). Philadelphia, PA: Elsevier.

Ohls, R. K. (2017). Developmental erythropoiesis. In R. Polin, S. H. Abman, D. Rowitch, W. Benitz, W. Fox, & W. William (Eds.), *Fetal and neonatal physiology* (5th ed., pp. 1112–1134). Philadelphia, PA: Elsevier. doi:10.1016/B978-0-323-35214-7.00116-5

Ohls, R. K. (2019). Red blood cell transfusions in the newborn. In M. S. Kim (Ed.), *UpToDate*. Retrieved from https://www.uptodate.com/contents/red-blood-cell-transfusions-in-the-newborn

Pacheo, L. D., Berkowitz, R. L., Moise, K. J., Bussel, J. B., McFarland, J. G., & Saade, G. R. (2011). Fetal and neonatal alloimmune thrombocytopenia: A management algorithm based on risk stratification. *Obstetrics and Gynecology, 118*(5), 1157–1163. doi:10.1097/AOG.0b013e31823403f4

Patel, R. M., & Josephson, C. D. (2018). Neonatal transfusion. In C. A. Gleason & S. E. Juul (Eds.), *Avery's diseases of the newborn* (10th ed., pp. 1180–1186.e3). Philadelphia, PA: Elsevier.

Pernoll, M., et al. (1986). Neonatal hyperbilirubinemia and prevention of kernicterus. In M. Pernoll, G. I. Benda, S. G. Babson, & K. Simpson (Eds.), *Diagnosis and management of the fetus and neonate at risk* (5th ed.). St. Louis, MO: Mosby.

Preer, G. L., & Philipp, B. L. (2011). Understanding and managing breast milk jaundice. *Archive of Diseases in Childhood, Fetal & Neonatal Edition, 96*, F461–F466. doi:10.1136/adc.2010.184416

Sacks, L., & Delivoria-Papadopoulos, M. (1984). Hemoglobin-oxygen interactions. *Seminars in Perinatology, 8*, 168–183.

Sallmon, H., & Sola-Visner, M. (2012). Clinical and research issues in neonatal anemia and thrombocytopenia. *Current Opinion in Pediatrics, 24*(1), 16–22. doi:10.1097/MOP.0b013e32834ee5cc

Saxonhouse, M. A. (2018). Neonatal bleeding and thrombotic disorders. In C. A. Gleason & S. E. Juul (Eds.), *Avery's diseases of the newborn* (10th ed., pp. 1121–1138.e4). Philadelphia, PA: Elsevier.

Schulman, I. (1962). Pediatric aspects of the mild hemophilias. *Medical Clinics of North America, 46*, 93–105. doi:10.1016/S0025-7125(16)33750-6

Shannon, K. M., Keith, J. F., 3rd., Mentzer, W. C., Ehrenkranz, R. A., Brown, M. S., Widness, J. A., . . . Phibbs, R. H. (1995). Recombinant human erythropoietin stimulates erythropoiesis and reduces erythrocyte transfusions in very low birth weight preterm infants. *Pediatrics, 95*, 1–8. Retrieved from https://pediatrics.aappublications.org/content/95/1/1

Shapiro, S. M. (2012). Hyperbilirubinemia and the risk for brain injury. In J. M. Perlman (Ed.), *Neurology: Neonatology questions and controversies* (2nd ed., pp. 163–180). Philadelphia, PA: Saunders. doi:10.1016/B978-1-4377-3611-3.00010-9

Stockman, J., Garcia, J. F., & Oski, F. A. (1977). The anemia of infancy and the anemia of prematurity: Factors governing the erythropoietin response. *New England Journal of Medicine, 296*, 647. doi:10.1056/NEJM197703242961202

Warren, M., Miller, A., Traylor, J., Sidonio, R., & Morad, A. (2013). Late vitamin K deficiency bleeding in infants whose parents declined vitamin K prophylaxis—Tennessee. *Morbidity, Mortality Weekly Report, 62*(45), 893–907. Retrieved from https://www.cdc.gov/mmwr/pdf/wk/mm6245.pdf

Watchko, J. F. (2015). Common hematologic problems in the newborn nursery. *Pediatric Clinics of North America, 62*(2), 509–524. doi:10.1016/j.pcl.2014.11.011

Watchko, J. F., & Tiribelli, C. (2013). Bilirubin-induced neurologic damage—Mechanisms and management approaches. *New England Journal of Medicine, 369*, 2021–2030. doi:10.1056/NEJMra1308124

Widness, J. A. (2008). Pathophysiology of anemia during the neonatal period, including anemia of prematurity. *NeoReviews, 9*(11), e520–e525. doi:10.1542/neo.9-11-e520

Winkelhorst, D., Oepkes, D., & Lopriore, E. (2017). Fetal and neonatal alloimmune thrombocytopenia: Evidence based antenatal and postnatal management strategies. *Expert Review of Hematology, 10*(8), 729–737. doi:10.1080/17474086.2017.1346471

Witt, S. (1948). *Hemostatic agents*. Springfield, IL: Charles C. Thomas Publishers.

Yoshimoto, M., & Yoder, M. C. (2017). Developmental biology of stem cells: From the embryo to the adult. In R. Polin, S. H. Abman, D. Rowitch, W. Benitz, W. Fox, & W. William (Eds.), *Fetal and neonatal physiology* (5th ed., pp. 1094–1104). Philadelphia, PA: Elsevier. doi:10.1016/B978-0-323-35214-7.00114-1

Zaiden, R. A. (2017). Hemophilia B. In S. Nagalla (Ed.), *Medscape*. Retrieved from http://emedicine.medscape.com/article/779434

Zwiers, C., Scheffer-Rath, M. E., Lopriore, E., de Haas, M., & Liley, H. G. (2018). Immunoglobulin for alloimmune hemolytic disease in neonates. *Cochrane Database of Systematic Reviews*, (3), CD003313. doi:10.1002/14651858.CD003313.pub2

CHAPTER 14

Musculoskeletal System

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INTRODUCTION

The human body is active, responsive, and constantly moving. The development of its functional motor skills is dependent upon the development of the musculoskeletal system. The musculoskeletal system comprises bones, joints, ligaments, muscles, bursa, fascia, and tendons. From an anatomic structural standpoint, infants, children, and adults differ in many ways: body size proportions, tissue thickness, body fat composition, bone density, muscle fiber type, joint structure development, muscle tone, posture, and bone, muscle, and ligamentous strength (Alexander, Boehme, & Cupps, 1993; Huelke, 1998; Hunter, Lee, & Altimier, 2015). For infants, the uterine environment functions to support and reinforce musculoskeletal symmetry, strength, physical stature, range of motion, and muscle tone (O'Brien, 2015). Flexible uterine walls assist in returning the infant from an extended posture to one that is flexed, midline, and supported circumferentially (Hunter et al., 2015). Additionally, the uterine environment supports hand-to-mouth activity, considered necessary for future participation in daily living activities such as feeding and playing.

This chapter provides a review of typical musculoskeletal development during the neonatal period and also describes musculoskeletal problems seen in the period. Collaborative management is discussed, as well as the long-term implications of the functional and aesthetic concerns encountered with musculoskeletal dysfunction.

EMBRYOLOGY

An extensive discussion of embryology is beyond the scope of this chapter; however, a brief review is provided. Prenatal development is divided into two stages: the embryonic period (first trimester) and the fetal period (second and third trimester) (Liu & Thompson, 2019). The embryonic period is characterized by maximal organogenesis and lasts from the end of the first week until the eighth week of gestation. Rapid cell division during organogenesis renders an organ vulnerable to any disturbance that might result in aberrant development. Functional and minor morphologic abnormalities may occur any time during gestation. The embryo originates from three cell layers: the ectoderm, the endoderm, and the mesoderm. The embryonic mesoderm gives rise to the articular, muscular, and axial and appendicular skeletal systems.

The articular system, or joints, can be classified into three types: fibrous, cartilaginous, and synovial. Fibrous joints are those in which two bones are separated only by dense fibrous connective tissue, as seen in cranial sutures. Cartilaginous joints (such as the symphysis pubis and between the intervertebral discs of the spine) have hyaline cartilage or fibrocartilage between the two bony surfaces. The elbow and knee are examples of synovial joints. In these joints, the adjoining bone ends are covered with a thin cartilaginous layer and joined by a ligament lined with a synovial membrane. Ligaments hold bones together; the capsule encases the joint to provide support and protection. The synovial membrane secretes a lubricant referred to as *synovial fluid*, a source of nutrition for the articular cartilage. Synovial joints are the most mobile, yet can withstand pressure and provide stability between the bones, especially during weight bearing. The articular system begins to develop during the sixth week of gestation, with functional joints being present by the end of the eighth week. Joints allow motion to occur. Box 14.1 lists common terminology used to describe types of motion and the planes in which motion occurs.

Muscle origin and insertion, muscle fiber arrangement, types of muscle contraction, arthro- and osteokinematics, muscle tissue, and movement characteristics are important for clinicians to consider Groups of myotubes, the primordia of skeletal or striated muscle, are apparent by the end of the eighth week of gestation. As the myotubes enlarge, the appearance of myofilaments is evident in interior regions. Growth of myofilaments leads to mature muscle fibers. Postnatal development of muscle fibers continues both in number and in size. Muscle development depends on proper innervation, evident at 8 to 10 weeks of gestation. Without this innervation, the muscles atrophy. The mother can detect intrauterine fetal movements at 16 weeks of gestation. Infants born prior to 31 weeks gestational age have immature muscle fibers, neuromuscular junctions, and diminished flexor tone. Muscle tone development occurs caudocephally, with lower extremity tone beginning at about 33 to 35 weeks post menstrual age and upper extremity tone increasing around 35 to 37 weeks (Byrne & Garber, 2013).

The skeleton develops by intramembranous bone formation and endochondral ossification. It gives shape and support to the body, protects vital organs, and provides structure for muscular attachments. Bones are soft, develop cephalocaudally, and are made up of several types of tissue (fibrous, cartilaginous, osseous, nervous, vascular). Upper limbs develop more quickly than the lower limbs, and several days elapse between the development of the

Box 14.1

JOINT MOTIONS AND PLANES OF MOVEMENT

- Abduction: movement in the coronal plane that moves a limb laterally away from the body
- Adduction: movement in the coronal plane that moves a limb medially toward or across the midline of the body
- Dorsiflexion: movement at the ankle that brings the top of the foot toward the anterior leg
- Eversion: foot movement involving the intertarsal joints of the foot in which the bottom of the foot is turned laterally, away from the midline
- Extension: movement in the sagittal plane that increases the angle of a joint (straightens the joint); motion involving posterior bending of the vertebral column or returning to the upright position from a flexed position
- Flexion: movement in the sagittal plane that decreases the angle of a joint (bends the joint); motion involving anterior bending of the vertebral column
- Horizontal abduction: holding arm at shoulder height, moving the shoulder backward
- Horizontal adduction: holding arm at shoulder height, moving the shoulder across body
- Hyperextension: continuation of extension beyond the normal range of motion
- Inversion: foot movement involving the intertarsal joints of the foot in which the bottom of the foot is turned toward the midline
- Palmar flexion: bending the wrist toward the palm
- Planes of Movement:
    - Sagittal plane (lateral plane): a vertical plane running from front to back; divides the body or any of its parts into right and left sides; extension and flexion motions occur in this plane
    - Coronal plane (frontal plane): a vertical plane running from side to side; divides the body or any of its parts into anterior and posterior portions; abduction and adduction motions occur in this plane
    - Axial plane (transverse plane): a horizontal plane; divides the body or any of its parts into upper and lower parts; rotation occurs in this plane
- Plantar flexion: movement of the ankle toward the surface of the foot
- Pronation: movement that combines eversion, dorsiflexion, and abduction
- Scapular abduction: shoulder girdle protraction, or rounding the shoulders forward
- Scapular adduction: shoulder girdle retraction, or squeezing the shoulder blades together
- Supination: movement that combines inversion, plantar flexion, and adduction
- Trunk/neck lateral bending: occurs to right and left sides
- Ulnar and radial deviation: hand movement toward little finger side and hand movement toward thumb side
- Wrist extension/dorsiflexion: bending the wrist away from the palm toward the lower arm

Sources: Betts, J. G., Desaix, P., Johnson, E., Johnson, J. E., Korol, O., Kruse, D., . . . Young, K. A. (2013). Anatomy & physiology (pp. 345–349). Houston, TX: Rice University. Retrieved from https://opentextbc.ca/anatomyandphysiology/chapter/9-5-types-of-body-movements; Lippert, L. S. (2011). *Clinical kinesiology and anatomy* (5th ed.). Philadelphia, PA: F. A. Davis; National Cancer Institute. (n.d.). *Anatomical terminology*. Retrieved from https://training.seer.cancer.gov/anatomy/body/terminology.html

upper limbs and that of the lower limbs. The vertebral column is initially of a cartilaginous form, with ossification beginning during the embryonic period and reaching completion in early adulthood. Ossification is evident in all long bones by 12 weeks gestation, with arms, legs, fingers, and toes typically recognizable at this stage. The fetal period represents a time of further growth and development. At birth, an infant's skeleton is primarily cartilaginous and made up of more than 300 bones. Throughout childhood and into adulthood, the infant's bones will fuse and ossify, resulting in the 206 bones typically seen in an adult skeleton.

POSITIONAL TERMINOLOGY

As an infant's body learns to move and reposition itself, it is imperative that clinicians understand the infant's motoric developmental sequence and the terms that describe those changes from anatomical position:

- Anterior/ventral: front of the body or a position close to the front
- Posterior/dorsal: back of the body or a position close to the back
- Medial: toward the midline of the body
- Lateral: away from the midline of the body
- Supine: lying on back; face is upward
- Prone: lying on stomach; face is downward
- Side lying: lying on side with neutral/midline orientation
- Distal: away from the trunk
- Proximal: toward the trunk
- Cephalo or cranial: close to the head
- Caudal: close to the feet
- Superior: refers to the position of a body structure above another
- Inferior: refers to the position of a body structure below another
- Superficial: position of relative depth; on top of
- Deep: position of relative depth; underneath
- Contralateral: refers to opposite side of body
- Ipsilateral: refers to same side of body
- Valgus: describes an abnormal position in which a distal body part is bent outward and away from the midline of the body
- Varus: describes an abnormal position in which a distal body part is positioned inward, toward the midline of the body
- Subluxation: incomplete dislocation or a displaced joint
- Dislocation: complete separation of one articulating joint surface from another
- Reduction: restoration of a body part to a normal position

MUSCULOSKELETAL ASSESSMENT

Maternal history is reviewed for uterine anomalies that may compromise fetal movement and growth, such as the bifid uterus, the division of the uterine cavity into two segments. Additional maternal and a family history that are important include family members, especially siblings, with musculoskeletal anomalies; presence of oligohydramnios (reduced amniotic fluid volume); and fetal movement during gestation and the birthing process.

Detailed observation is the key tool for assessing the neonatal musculoskeletal system. Visual inspection should begin in one body region—that is, cephalic or caudal—and progress along the body in an organized fashion from proximal to distal. For the initial examination, place the infant in a quiet resting state to assess posture, positioning, and identification of any obvious anomalies.

Box 14.2

MUSCULOSKELETAL CONDITIONS

- Arthrogryposis multiplex congenita, or multiple congenital joint contractures
- Congenital upper and lower limb defects, which can be caused by maternal exposure to known risk factors, genetic abnormalities, growth restriction, mechanical forces, and so forth
  - Absence of limbs
  - Amniotic band syndrome: occurs when tears in the amnion get wrapped around digits, limbs, or other parts of the body
  - Congenital talipes equinovarus: *clubfoot*
  - Syndactyly: fingers and/or toes that failed to separate
  - Polydactyly: duplication of fingers and/or toes
  - Undergrowth or overgrowth of limbs
- Fractures and/or bowing of bones
  - Birth trauma
  - Greenstick fracture: occurs when one side of bone is broken and the other bent
  - Epiphysis/growth plate fracture
  - Bowing: angular deformity of bones, typically long bones
- Hip dysplasia or dislocation: instability of the femoral head in the acetabulum, allowing the hip joint to become partially or completely dislocated
- Positional deformities
  - Intrauterine
  - Acquired, from prolonged hospitalization
  - Home based/post discharge: examples include torticollis, plagiocephaly, hip contractures
- Orofacial clefts: incomplete closure of the palate and/or lip
- Craniosynostosis: premature closing/fusion of the fibrous cranial sutures
- Plagiocephaly: misshapen head (Bialocerkowski & Vladusic, 2008)
  - Brachycephaly: wide, flattened back of head
  - Dolichocephaly or scaphocephaly: long, narrow head
- Structural disorders of the spine
  - Spinal deformities
    - Kyphosis: abnormally rounded upper back
    - Scoliosis: spine is curved sideways
    - Lordosis: excessive in-curving at the base of the spine, or *swayback*
  - Torticollis: congenital, positional, birth injury; tightness of the neck musculature causing the head to tilt to one side and rotate to the other
- Skeletal dysplasias: bone and cartilage disorders affecting the fetal skeleton
  - Achondroplasia: *dwarfism* or short stature
  - Hypochondroplasia
  - Thanatophoric dysplasia
  - Osteogenesis imperfecta congenita: *brittle bone disease*
  - Thrombocytopenia-absent radius syndrome

Active movement by the infant allows the clinician to view muscle tone and active ranges of motion. Manipulation is used to assess passive range of motion, including joint mobility. Caution should be taken when assessing infant range of motion, as it is often a stressful and potentially painful or harmful experience for the neonate. Radiologic studies as well as simple body measurements aid the healthcare provider in the identification of covert or hidden musculoskeletal deformities such as hip dysplasias and the absence of bony structures.

In developing a differential diagnosis, the clinician must be aware that a combination of deformities present in a neonate may be a small part of a larger syndrome. Conversely, congenital anomalies that present in combination may be a coincidental finding (Box 14.2). Musculoskeletal conditions may be accompanied by acute and/or chronic pain, limitations in mobility, decreased functional ability, and reduced dexterity (World Health Organization, 2018).

TYPES OF MUSCULOSKELETAL DYSFUNCTION

Abnormalities of the neonatal musculoskeletal system can range from a subtle brachydactyly (shortened fingers or toes) to congenital amputation, to a fatalistic form of osteogenesis imperfecta (OI) congenita. Causes range from uterine malpositioning of the fetus to autosomal dominant disorders. Neurologic, infectious, and/or genetic conditions can affect musculoskeletal development, as can post-procedural disorders of the musculoskeletal system (e.g., birth trauma). Regardless of the clinical significance, an overt structural defect can become the focus of parental attention. Assessment of the musculoskeletal system—which can have multiple normal variants—and knowledge of pathogenesis, sequelae, treatment, and prognoses for deformities of this system are imperative to the clinician. Delay in diagnosis and treatment may be implicated as a cause of a less than favorable outcome of the musculoskeletal deformity. Deformities of the musculoskeletal system create not only functional problems but, in some cases, visible defects as well. The type of dysfunction may greatly affect how the parent views the neonate and the infant's potential for positive growth and development. Appropriate education of the family by the healthcare professional is often paramount to a beneficial outcome because many musculoskeletal disorders require compliance with long-term therapy.

ARTHROGRYPOSIS MULTIPLEX CONGENITA

Historically, the term *arthrogryposis* (curved, hooked joint) has been used not only to provide a description of a clinical appearance but also as a diagnosis for various conditions (Figure 14.1). As a group of conditions, arthrogryposis multiplex congenita is considered rare, occurring in 1 out of every 3,000 to 12,000 births.

FIGURE 14.1 Distal fixed joints: arthrogryposis.

The common denominator for more than 400 known conditions is the presence of multiple congenital joint contractures and is typically characterized by decreased fetal movement (Lakhani et al., 2017). Many of these conditions are syndromes unrelated to a chromosomal or genetic problem.

Pathogenesis

Classic arthrogryposis (also termed *amyoplasia*) describes limitation of movement in multiple joints that is present at birth. In distal arthrogryposis, the hands and feet are involved but larger joints are spared (Kimber, 2015). Due to the variety of comorbidities that may be associated with these conditions, the etiology is varied. With decreased movement, extra connective tissue forms around the joints of the fetus and fixes them in position. This may be related to abnormal development of the muscles, tendons, and/or joints as listed in Table 14.1. In some cases, the fetus may be prevented from normal movement due to restrictions within the uterus from multiple pregnancies or abnormalities of the uterine structure. Maternal diseases, such as myasthenia gravis or myotonic dystrophy, may be related to arthrogryposis, as well as the use of certain medications or infections in the mother. Intrauterine vascular compromise is another potential associated factor, with damage to developing muscles and nerves due to decreased blood flow (O'Flaherty, 2001). Finally, abnormalities of the central nervous system (CNS) in the fetus may be a cause, such as spinal muscle atrophy or cerebro-oculo-facial-skeletal syndrome (Table 14.1).

Clinical Manifestations

Arthrogryposis is characterized by limited movement of the affected joints. The distal joints are more frequently affected than proximal joints. Talipes equinovarus (clubfoot) is almost universal, and the wrists are typically flexed. The elbows and knees can be in a flexed or extended position. Dimpling may be noted at the elbows and knees. Shoulders are internally rotated. Normal skin creases overlying the joints are often absent, suggesting an onset of arthrogryposis in the early intrauterine period. Changes in facial features may also be seen, including micrognathia (an undersized chin, which can interfere with breathing and eating).

Diagnosis

A thorough evaluation is required to determine the cause of arthrogryposis. This process may begin prenatally. Decreased fetal movement and joint contractures are often seen on prenatal ultrasound. Polyhydramnios may be seen secondary to decreased fetal swallowing. Prenatal imaging may reveal other physical characteristics that lead to suspicion of certain syndromes. Amniocentesis may provide information leading to a genetic diagnosis. **Quality and Safety: A detailed family history is essential to detect evidence of an inherited disorder. Maternal pregnancy and labor/delivery history should be reviewed carefully.** Physical examination of the infant with careful description of the affected joints is needed, as well as detailed evaluation of the muscle mass and tone and function of the nervous system. Radiographic and ultrasound evaluation is needed to determine the presence of other congenital anomalies, as this may help link the contractures to a specific syndrome. Detailed imaging of the brain and spinal cord is indicated. Muscle biopsy and nerve conduction tests may be recommended. Genetic testing is also required. If a specific genetic etiology or specific syndrome is detected, a more accurate assessment of long-term prognosis can be made.

TABLE 14.1

ETIOLOGY OF DECREASED FETAL MOVEMENT

Category	Examples
Myopathic	
Abnormal muscle function secondary to failure of muscle formation or degeneration	Congenital muscular dystrophy Absence of muscles
Neuropathic	
Abnormal nerve function or innervation that involves either CNS or the peripheral nervous system	Drugs or toxins CNS malformations: decreased number of anterior horn cells
Abnormal connective tissue	Abnormal formation of bone, cartilage, tendons, or connective tissue
Mechanical Limitation	
Produces compression within the uterus	Twins; Multiples Amniotic rupture Oligohydramnios Benign uterine myomas

CNS, central nervous system.

Management

Excluding infants with severe CNS dysfunction, infants with multiple congenital contractures have a good prognosis. The goal of management is to achieve and maintain an acceptable range of motion in the affected joints. During the newborn period, it is often a challenge to hold and care for these infants due to the extended or flexed position of the extremities and the reduced ability to manipulate the contracted limbs. Occupational and physical therapy should be initiated early in the neonatal period, to begin strengthening muscles, improving range of motion, and addressing challenges to daily living activities (occupations). Splints and casts may be implemented, specifically molded and shaped for each limb depending on the severity of contractures and positioning (Figure 14.2). Occupational and physical therapy may be a lifelong process, and parents can be taught techniques to use with the child.

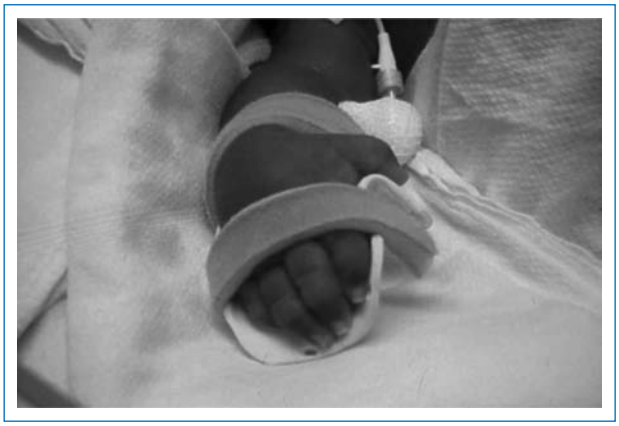

FIGURE 14.2 Hand splint with arthrogryposis.

FIGURE 14.3 Amniotic band constriction ring on the arm of a neonate.

Family involvement is a key factor in the success of therapy for these infants. Creativity on the part of the healthcare professional, as well as on the part of the parents, complements efforts to manipulate the rather rigid infant during feedings, sleeping, holding, and daily care activities. Parents may need referrals to agencies providing respite care or assistance from volunteers to maintain daily care needs.

Prognosis

The long-term prognosis for multiple congenital contractures depends on the extent of involvement. Mortality rates are low for those without CNS involvement (1%–7%). For those with CNS involvement, mortality rates rise to almost 50%. Ventilator dependence at birth is associated with a poor prognosis (Bianchi & Van Marter, 1994).

AMNIOTIC BAND SYNDROME

Amniotic band syndrome (ABS, also referred to as amniotic rupture sequence or constriction band syndrome) is associated with asymmetric fetal deformities due to entanglement of the infant in fibrous amniotic bands. Deformities that have been attributed to the ABS include congenital limb amputation, syndactyly, constriction bands, clubfoot, craniofacial defects such as cleft lip and palate, and visceral defects such as gastroschisis and omphalocele (Baraitser & Winter, 1996). Early fetal evaluation has linked ABS with skull and brain defects (S. H. Lee, Lee, Kim, Son, & Namgung, 2011). **Emergency Alert: ABS can be fatal if organs are involved.**

Pathophysiology

Etiologic factors in ABS are unclear. Part of the difficulty is that some of the same deformities that occur with this syndrome can also occur for other reasons. Thus, the exact cause of the deformities is not always clear, but the primary theory is the association with early amnion rupture and fetal entanglement of the resulting fibrous bands.

Two theories—endogenous and exogenous—explain the cause of ABS. The endogenous theory postulates that the deformities are caused by an innate derangement of the primary embryonic cell layers from which the tissues and organs develop. The presence of amniotic bands, according to the endogenous theory, is a late development with no clinical significance.

The exogenous—and seemingly more popular—theory contends that early amniotic rupture allows the fetus to move into close approximation to the chorion by entering the chorionic cavity. The ruptured amnion then forms fibrous strings or bands. These bands can adhere to the skin, thus altering normal morphogenesis (e.g., cleft lip or palate, omphalocele), or disrupt the vascular integrity, resulting in gastroschisis. Amniotic bands have been found encircling normally developed structures, thus resulting in congenital amputations, constriction rings with lymphedema distal to the ring, and facial clefts in nonanatomic distribution. Postural deformities such as clubfoot are believed to be caused by the fetus's close approximation to the chorion.

Figure 14.3 is an example of an amniotic band constriction ring noted on the arm of an infant with unilateral cleft lip and palate. Evidence of this constriction ring indicates that development of the lip and palate were at one time normal, but development was altered with the presence of amniotic bands.

Diagnosis

Many clinicians believe that amniotic bands must be present for ABS to be diagnosed. Others, however, believe that the presence of fetal deformities in a nonanatomic pattern, without obvious bands, is sufficient to establish the diagnosis of the syndrome. Congenital deformations, such as the visceral and craniofacial types, in the absence of amniotic bands may go undiagnosed as ABS because they could represent a faulty midline developmental pattern during the first trimester of pregnancy instead of the production of amniotic bands that constricted or restricted growth. The true incidence of this syndrome, therefore, may be much higher than it generally appears—not only because of the difficulty in establishing a diagnosis but also because of the high mortality rate that exists during gestation.

ABS has been implicated in fetal deaths secondary to cord compression by the constricting bands. Strauss, Hasbargen, Paek, Bauerfeind, & Hepp (2000) provide a clinical report of fetal demise involving a normal karyotype male secondary to torsion and strangulation of the umbilical cord by an amniotic band. The only significant history in the gestation was an early second-trimester amniocentesis. It has been speculated that amniotic rupture may follow amniocentesis and fetal blood sampling. Strangulation furrows, limb reduction defects, and cleft lip or palate can be late sequelae of invasive prenatal procedures in animal models.

Collaborative Management

Notwithstanding the inherent problems associated with omphaloceles, gastroschisis, encephaloceles, clubfoot, syndactyly, and facial clefts, the clinician must be attuned to the unique complications

of constricting bands. Constricting bands are usually associated with edema distal to the band. The resulting edema and vascular compromise contribute to complications such as skin breakdown, necrosis, thromboembolic formation that results from venostasis, and infection. **Quality and Safety: Care should include frequent vascular checks to assess perfusion. Trauma and tissue breakdown are discouraged through positioning and skin care. Observation for localized areas of necrosis is stressed.**

As with other musculoskeletal disorders, the family may require emotional and psychological support as adjustment to and acceptance of the infant are allowed to occur. Parents may be fearful that an extremity will be lost because of necrotic tissue formation or infection. These fears may be justified, and the parents should be prepared for such a possibility. Complete surgical repair may not be possible during the infant's initial hospitalization, thus necessitating frequent hospitalizations during the early developing years. The delay in repair may necessitate that parents be taught to observe for vascular perfusion of an extremity, to recognize signs of infection, and to change dressings over open or healing areas. Preparation for discharge requires a multidisciplinary approach. The family may need surgical supplies, follow-up visitations by a home-visiting nurse, orthopedic or surgical consultations, pediatrician visits for general well-child care, and support of social or financial services to meet the long-term responsibilities of caring for their infant.

In addition, the nurse, working in collaboration with pediatric occupational therapists and social workers, must attempt to provide opportunities for parent–infant bonding if the parents are to feel somewhat prepared for discharge. While the infant is still in the hospital, the parents must be encouraged to touch and talk to the infant and to participate in the infant's care. They must also be encouraged to verbalize their own feelings about their infant's condition. Every attempt should be made to attend to their fears, concerns, or misconceptions about the cause of their infant's problem.

CLUBFOOT

The classic clubfoot, talipes equinovarus, refers to a dysmorphic-appearing foot with hindfoot equinus (heel is pulled upward as if walking on the toes), forefoot adduction (toes are pointed inward), and midfoot supination. The term *clubfoot* may also be used to describe milder talipes conditions, including talipes calcaneus and talipes varus.

Foot deformities are among the most common birth defects. Clubfoot has an incidence of 1 in 1,000 live births. Males are affected nearly twice as often as females, and, in infants with unilateral presentation, the majority appear on the right.

Pathology

The precise mechanism of development of clubfoot has not been irrefutably established. Some researchers allude to the theory of intrauterine malposition, whereas others, noting a higher incidence of clubfoot in families with a positive history of the disorder, ascribe it to a genetic cause. A popular theory is that clubfoot is a multifactorial disorder involving a genetic predisposition coupled with environmental forces such as oligohydramnios, primiparity, macrosomia, and multiple fetuses.

Clinical Manifestations

Clubfoot deformities are apparent at birth. The skin overlying the lateral aspect of the foot may be taut, whereas the medial aspect may have increased skin folds. The affected foot may be smaller in size than a normal foot. In older children, the calf muscle may be noticeably decreased in size. Milder talipes conditions may be returned to the neutral position by manipulation. The potential for pain also must be addressed.

Collaborative Management

Early diagnosis by orthopedic specialists and treatment referrals to physical and occupational therapists is essential. In the early newborn period, joints, muscles, and ligaments may be more compliant to corrective manipulation without surgical intervention. This may involve serial casting or initiation methods of correction and maintenance such as the Ponseti method (Smythe, Mudariki, Kuper, Lavy, & Foster, 2017). **Emergency Alert: Difficulty with skin closure has been reported as a complication following correction of severe clubfoot.** This is especially true if the affected foot has received prior surgery. Special shoe splints or braces may be used toward the end of any successful treatment.

Parental education includes implementation of routine newborn care for an infant wearing either splints or bilateral casts. Problems and solutions associated with clothing, sleeping, feeding, and bathing should be addressed. Compliance by parents in using splints may vary. Because consistent treatment is necessary for a favorable outcome, healthcare professionals must explore parental feelings and actions while providing anticipatory guidance.

SYNDACTYLY

Fusion, or webbing, between two digits is referred to as *syndactyly*. This condition is the most common anomaly of the hand, with an incidence of 1 in 2,250 live births. Males are affected slightly more than females. Half of the time, both hands are involved in a symmetric presentation. Syndactyly of the fingers may be accompanied by syndactyly of the toes.

Pathology

Although most occurrences of syndactyly appear to be through spontaneous mutation, familial predisposition has been reported, thus indicating an autosomal dominant pattern. Syndactyly may also be associated with a specific syndrome such as Apert syndrome.

There are four classifications of syndactyly. Complete syndactyly occurs when the fusion is from the base to the tip of the digit. Fusion that does not extend to the tip of the digit is termed incomplete. Simple syndactyly refers to digits connected by skin and soft tissue. Fused digits involving an osseous connection are considered complex. Abnormal nerve and vessel configurations may accompany complex syndactyly.

Treatment

The type and timing of treatment of syndactyly depend on its classification. Surgery is directed toward promoting normal function and appearance. Fingers of unequal length should be separated within 6 to 12 months of age to prevent curvature of the longer finger from deviating toward the shorter finger. If more than two adjacent digits are involved, surgery should be performed in stages to prevent vascular compromise of the middle digits.

Prognosis

Prognosis is favorable for normal function and appearance, except in cases of complex syndactyly involving not only bone but also vascular and nervous tissue. These cases may be associated with some postoperative loss of function.

Collaborative Management

Parents of infants with syndactyly are instructed in occupational and physical therapy, specifically in massage of the interconnecting skin. Massaging of the webbed area prior to surgery allows some stretching of the skin, which permits easier repair. Referrals to certified hand therapists or plastic surgeons may also be indicated.

POLYDACTYLY

Polydactyly is any duplication of digits beyond the typical five. It is the second most common hand anomaly, next to syndactyly. Polydactyly is believed to be caused by duplication of a single embryonic bud. African Americans are affected 10 times more often than Caucasians. African Americans more often have postaxial polydactyly (duplication of the little finger), whereas preaxial polydactyly (duplication of the thumb) occurs primarily in Caucasians. In African Americans, postaxial polydactyly is typically an isolated incidence, whereas in Caucasians it is associated with syndromes and chromosomal anomalies. Central axial polydactyly is the duplication of the ring, long, or index finger. Central axial polydactyly is often associated with complex syndactyly. Polydactyly may be further classified into three types: Type I is merely a rudimentary soft tissue mass connected by a piece of tissue, or pedicle. Treatment of this type involves simple excision, which can typically be done prior to discharge from the nursery per the parents' request. To avoid any residual skin tag after excision, infants are often referred to plastic surgery for a more complete removal. Type II is a partial duplication with involvement of the phalanges. Type III, a rare occurrence, involves complete duplication of the metacarpal and phalanges.

Collaborative Management

Treatment of polydactyly types II and III centers around functional capacity first and appearance second. The infant is observed for which duplication is dominant and most functional, and efforts are made to remove the least functional counterpart. If both duplicated digits appear to be equally functional, surgery should then be used to promote aesthetic appearance. Reparative surgery often begins prior to 18 months and should be completed by 3 years of age.

BIRTH TRAUMA

Birth trauma encompasses both mechanical and asphyxial events occurring during delivery. This trauma may be due to pressure and distortion. Mild, transient, or disabling trauma can occur despite exemplary obstetrical care; encouragingly, birth trauma rates are declining but still occur in approximately 2.6% of live births (Chaturvedi, Chaturvedi, Stanescu, Blickman, & Meyers, 2018). A positive association exists between birth trauma and macrosomia, prematurity, breech presentation, shoulder dystocia, cephalopelvic disproportion, and vacuum extraction.

Clinical Manifestations

Birth trauma includes subdural and intracerebral hemorrhage, abrasions, ecchymoses, erythema, cephalohematomas, caput succedaneum, fractures (especially of the clavicle), skeletal and spinal cord injuries, brachial plexus damage, and nerve palsies. Clavicular fractures are the most common fractures diagnosed as birth trauma. Clavicles are at an increased risk for fractures during shoulder dystocia in a vertex presentation or with arms extended during a breech delivery (Liu & Thompson, 2019).

Quality and Safety: Physical examination findings related to birth trauma may appear only as bruising, abrasions, and petechiae that overlie the affected part. Further diagnostic methods should be used when the infant exhibits pain on movement, limited motion, and abnormal passive positioning of an extremity or head movement.

Skull fractures may present as cephalohematomas. Skull fractures are most often linear and typically involve the parietal bones. Symptomatic evidence of a nondepressed skull fracture may resemble signs of increased intracranial pressure secondary to epidural hemorrhage. Clinical presentation may include changes in muscle tone, hypertonicity or hypotonicity, arching of the back with the head in hyperextension, and respiratory compromise. Usually, no treatment is indicated for asymptomatic skull fractures. Depressed skull fractures, however, may require elevation of the depressed area.

Emergency Alert: A rare, but possible, fatal delivery complication is subgaleal hemorrhage. This may present as a cephalohematoma with a small area of swelling on the scalp as early as 4 hours of age. This often progresses and, unlike the cephalohematoma, crosses suture lines and involves the nape of the neck. The volume of blood loss may be high, causing hypovolemic shock.

Vertebral fractures are incurred in difficult breech deliveries in which longitudinal traction in combination with a twisting motion may occur. These features commonly involve the seventh cervical and first thoracic vertebrae. Treatment depends on the extent of resultant nerve damage but often requires traction.

The most common nerve injury attributed to birth trauma is brachial plexus damage and resulting nerve palsy. This injury involves damage to the network of nerve fibers in the neck and shoulders referred to as the *brachial plexus*. The prognosis is variable: Up to 35% of children with brachial plexus palsy may demonstrate lasting functional impairment of the involved limb (O'Berry, Brown, Phillips, & Evans, 2017). Involvement may occur in the upper portion (Erb–Duchenne palsy), lower portion (Klumpke's paralysis), or both portions (complete brachial plexus palsy).

Erb–Duchenne paralysis is the most common form. The affected arm is limp and in a position of elbow extension and internal rotation. The Moro reflex is diminished and the grasp reflex intact. Klumpke's paralysis involves paralysis of the hand and wrist and is uncommon in infants. Complete brachial plexus paralysis results in paralysis of the entire arm. With full nerve-root avulsion injuries, some sensory recover may occur but no motor recovery can be expected (Liu & Thompson, 2019).

Diagnosis

Diagnosis of birth trauma is based on physical assessment findings. These are usually fairly visible at birth or in the immediate postnatal period. Physical findings should be confirmed, when necessary, by radiologic evaluation to establish whether a fracture is present. For significant scalp swelling, evaluation of the skull by x-ray is prudent.

Collaborative Management

Treatment of birth trauma depends on the type and severity of the trauma. Often, supportive measures may be the only intervention required. For instance, brachial plexus injuries may require immobilization in a neutral position using braces or splints. Specialized treatment protocols may, however, be initiated by occupational and physical therapists under the direction of pediatric orthopedic and/or neurology specialists. Surgery may also be indicated in severe cases.

Clavicular fractures also respond to supportive management. Typically, the arm is flexed, and the elbow is held against the chest. This position limits movement, thereby decreasing pain and

preventing additional trauma at the site. Callus formation stabilizes the fracture by 10 days of age. A hard, palpable knot can often be felt with this callus formation. Again, referral to orthopedists and occupational and/or physical therapists is indicated.

Parental Education and Support

Diagnosing a disorder resulting from birth trauma can evoke anxiety in a parent. Birth trauma may connote thoughts of violence. The manner in which such information is taken from and conveyed to the family is important. Nonjudgmental, supportive care by health professionals along with consistent primary care by one individual may diminish some anxiety and allow the parents to establish trust. The mother may especially feel that she is to blame for the neonatal problem. Calm reassurance about the nature of the trauma is important. It also helps to allay fears that something was done incorrectly during the delivery process if parents understand that many of these injuries cannot be avoided or anticipated. Parental education is prerequisite if the parents are to understand the need for continued, long-term treatment, which many of these infants require. Many birth trauma injuries require long-term follow-up care by orthopedists, neurologists, or occupational or physical therapists.

DEVELOPMENTAL DYSPLASIA OF THE HIP

Developmental dysplasia of the hip (DDH) refers to any manifestation of hip instability, ranging from subluxation to complete dislocation. DDH remains a common problem despite almost universal neonatal screening. Although controversy surrounds the usefulness of clinical neonatal screening programs for the diagnosis of DDH, these programs have led to earlier diagnosis and treatment for many infants. Additional studies have noted improved diagnosis of hip dysplasia with the use of ultrasound. It is recognized that up to 88% of unstable hips will normalize without treatment. Early clinical exams and targeted ultrasounds for infants with high-risk factors are the primary screening tools currently used. Infants with high-risk factors include those with a family member with congenital/developmental hip dysplasia, those with breech presentation, and those with feet deformities (Shorter, Hong, & Osborn, 2011).

Incidence and Risk Factors

Reports of the incidence of DDH vary. The incidence of DDH in the United States is approximately 1 to 4 in 1,000 live births. Differences in DDH incidence rates across ethnic groups can be attributed to genetic, ethnic, and environmental influences. Other influential factors include the age of the infant at the time of examination, the expertise of the examiner, and the definition used by the examiner for the diagnosis of DDH.

Incidence of DDH is increased in first-born children. This increase may be due to the unstretched uterine and abdominal muscles, oligohydramnios, and the high association of fetal breech positioning in primigravidas. A definite preponderance toward DDH occurs in female children. The ratio of occurrence of DDH in girls to boys is 6 to 1. Females account for 80% of all cases of DDH. Factors that may contribute to this finding include the fact that twice as many females as males present in the breech position, and females appear to have heightened laxity in response to maternal relaxin hormones.

Breech position remains a major contributory factor to the development of DDH. Specific incidences of DDH in relation to positioning are 0.7% for cephalic, 2% for footling, and 20% for single breech. The incidence of DDH for infants in the breech presentation is not altered by delivery methods. Breech-positioned infants delivered by cesarean section have the same predisposition to hip dislocation as those delivered vaginally. The left hip is involved three times more often than the right hip. Approximately 60% of DDH is on the left side, 20% on the right side, and 20% bilateral. This finding is attributed to the tendency of the fetus to lie with its left thigh against the maternal sacrum. This position forces the left hip into a posture of flexion and adduction. Thus, the femoral head is covered more by the joint capsule than by the acetabulum (Figure 14.4).

For infants born with other musculoskeletal and congenital renal abnormalities, such as torticollis and Potter's association, the incidence of DDH is increased. Congenital renal abnormalities can result in fetal oliguria (abnormally small amounts of urine), thus subsequently producing oligohydramnios. Oligohydramnios can cause postural deformities because of the mechanical pressure on the fetus. Torticollis, arthrogryposis, and metatarsus adductus are thought to result from intrauterine compression, as does DDH.

After 40 weeks gestation, the femoral head in the typically developing infant is firmly seated in the acetabulum and remains positioned there by the surface tension of the synovial fluid. The hips of the infant are difficult to dislocate. Conversely, the infant with a dysplastic hip has a loosely fitting femoral head and acetabulum. Because of this pathophysiologic phenomenon, the femoral head can assume several abnormal positions in an infant with DDH. One such position is termed *subluxation*. Subluxation occurs when the femoral head can be moved to the edge of the acetabulum but not completely out of it. Another position is termed a *dislocatable hip*. A dislocatable hip exists when the femoral head can be displaced from the acetabulum by manipulation but returns to the acetabulum afterward. The femoral head can also be found in a completely dislocated position at birth (Figure 14.5). Dislocated hips may or may not be reduced by manipulation.

DDH is a dynamic disorder that may improve or deteriorate with or without treatment. Thus, the joint may spontaneously dislocate and reduce (return to normal position) with normal neonatal movement. With time, this simple mechanism progresses in complexity secondary to adaptive changes. DDH can eventually progress either to permanent reduction, complete dislocation, or dysplasia (abnormal development). More than 60% of infants with hip instability stabilize within the first week of life, and 88% stabilize postnatally within the second month. Only 12% of infants with initial hip instability are considered to have DDH with potential for progression.

When complete dislocation occurs, pathologic changes occur to the femoral head, acetabulum, and ilium. This complete dislocation is due to the adaptive changes that occur in the

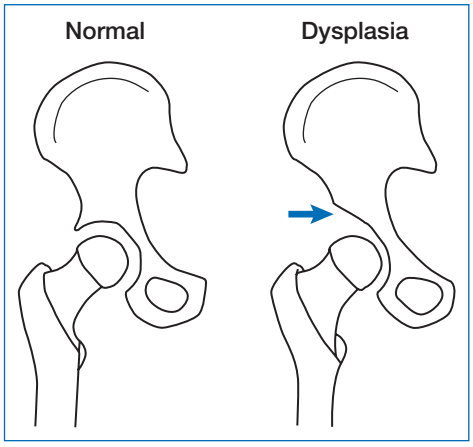

FIGURE 14.4 Acetabular dysplasia of the hip.

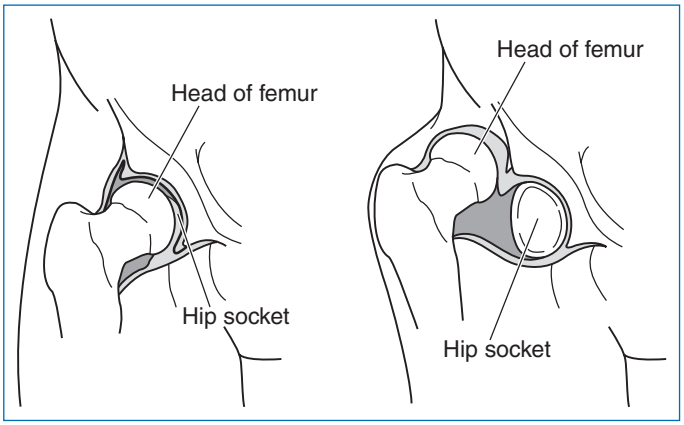

FIGURE 14.5 Normal position of the femoral head and hip socket (left), and hip dislocation (right).

adjacent tissue and bone. **Quality and Safety: The long-term complication of dislocation, when adequate treatment has not occurred, is degenerative changes of both the femoral head and the acetabulum. Once adaptive changes occur, risk for progressive degeneration despite treatment increases.** The subluxated hip, when not diagnosed in the neonatal period, is generally diagnosed at adolescence, when the strain of puberty and rapid growth spurts occur. With subluxation, the femoral head is laterally displaced and pushed upward into the joint; it is not completely out of the acetabulum. As the child grows and increased weight bearing occurs, the femoral head slides around and moves to the joint's edge. Degenerative changes result from this continual sliding. Early arthritis is a common complication in those with DDH, often requiring surgical intervention for improved mobility (Stelzeneder et al., 2012).

Diagnosis and Clinical Manifestations

In the neonatal period, the Ortolani and Barlow maneuvers are useful in diagnosing DDH (Williams, Protopapa, Stohr, Hunter, & Roposch, 2016). The Ortolani test is used to determine dislocation in the hip of a newborn, and the Barlow test is used to determine whether the hip is dislocatable (Barlow, 1962; Ortolani, 1976). In practice, both procedures are done in sequence. For examination, the infant is placed on a firm surface in the supine position.

The infant should be relaxed and quiet. Only one hip should be examined at a time. To perform the Ortolani test, the clinician stabilizes the infant's pelvis with one hand and with the other hand grasps the infant's thigh on the side to be tested. The examiner's middle finger is located over the greater trochanter (lateral aspect of the upper thigh), and the thumb is across the knee. The infant's hip is flexed to 90° while bending the knee. The infant's leg is then gently abducted with an anterior lift. In a positive Ortolani test, a *clunk* is heard with abduction. This clunk occurs as the dislocated femoral head slides over the posterior rim of the acetabulum and into the hip socket. Next, the hip is adducted, and, for the infant with DDH, a second clunk can be heard as the femoral head is displaced out of the acetabulum.

False-positive diagnoses of DDH have occurred when the examiner misinterprets a normal *click* (high-pitched sound) for a clunk. A click is not a sign of DDH. Clicks may be heard as a result of snapping of ligaments or tendons, and the majority are normal.

Barlow's test determines instability of the hip and identifies those hips that can be dislocated upon manipulation. Both hips and knees are flexed, with the hip to be tested in slight adduction. The examiner's middle finger remains positioned as for the Ortolani test, over the greater trochanter. The thumb is, however, located over the medial aspect of the infant's lower thigh. Gentle pressure is exerted by the thumb posteriorly and laterally (down and out). For the infant with DDH, the femoral head can be felt to move out of the acetabulum with the typical clunk. The hip can then be reduced by the Ortolani maneuver or simply by releasing thumb pressure and abducting and flexing the hips.

When the femoral head is subluxated, the examiner may observe a sliding motion in the hip joint during physical examination. This sliding motion can be characteristic of an unstable hip joint. Most cases of unstable hips spontaneously resolve without treatment.

The American Academy of Pediatrics (AAP) committee on quality improvement has issued guidelines to assist in the diagnosis and management of the infant with DDH. All newborns should receive a screening exam. The Barlow and Ortolani maneuvers are not useful after 8 to 12 weeks of age. Ultrasonography is not recommended as a universal screening tool but is useful as a targeted screening tool. If the physical exam of the neonate is equivocal, a repeat exam should be performed at 2 weeks of age. Certain physical signs that would result in an equivocal hip exam for DDH would include a persistent soft click. If the Ortolani/Barlow exam is positive with a hip clunk at 2 weeks of age, a referral to an orthopedic specialist is required. This is not an emergency but should be completed in a timely matter over the next few weeks. The infant presenting at 2 weeks with a persistent soft click should receive ultrasonography of the hip within the next 3 to 4 weeks or referral to an orthopedic specialist at this time. For the infant who exhibits a normal hip exam with resolution of the soft hip click, routine screening with well-baby checks during the first year of life is the recommendation. It is important to note that, according to the AAP recommendations, a newborn who is discharged before 48 hours of age should receive a repeat hip exam 2 to 4 days after discharge.

If the family has a history of DDH, the incidence increases to 9.4/1,000 in males and 44/1,000 in females. Because of this increased risk, even with a negative hip exam, an ultrasound at 6 weeks should be considered, or an x-ray of the hips at 4 months can be an alternative (Morey, 2001).

Collaborative Management

The goal of collaborative management is to achieve and maintain reduction of the unstable hip. The sooner treatment is implemented, the greater the chance for successful outcome. Various splinting devices are used to treat DDH in infants. Examples of splints include the Pavlik harness, von Rosen splint, Denis Browne hip adduction splint, and Frejka pillow splint. The most commonly used splint for neonates is the Pavlik harness.

The Pavlik harness allows for spontaneous hip and lower extremity movement while maintaining reduction of the hip joint. It can be worn comfortably during all aspects of newborn care, including diaper changes. The Pavlik harness can be adjusted for growth. It is indicated for use in newborns and infants up to 6 months of age. Use of the Pavlik harness is contraindicated for infants able to stand and for those infants in whom the hip joint is not reducible by manipulation. A major factor influencing the success of the Pavlik harness is parental compliance with the treatment. With this condition extensive parental education is imperative.

Parent and Family Education and Support

In addition to providing information regarding the pathology and treatment goals of DDH, the nurse should provide the parents with an opportunity to remove and reapply the harness while

under supervision. Referrals to physical therapy and/or occupational therapy may also be indicated. Parental support groups can help parents adjust to the infant's temporary awkward condition. Parents should also be educated in the procedure used to reduce the dislocated hip because complete reduction must be achieved before the harness is applied.

Long-Term Consequences and Complications

As with most therapeutic treatments, the potential for iatrogenic complications exists. Complications observed following DDH treatment include avascular necrosis, redislocation, and acetabular dysplasia. Complications can result from either inadequate or overly aggressive treatment. **Quality and Safety: Delaying surgery is also associated with poorer clinical outcomes, including limited range of motion, gait disturbances, and possible radiologic abnormalities** (Alnamshan, Jawadi, Alshoaibi, & Moukaddem, 2018).

Emergency Alert: An additional complication that has been reported with the use of the Pavlik harness is the development of brachial plexus palsy (Mostert, Tulp, & Castelein, 2000). The tension of the shoulder harness appears related to this complication. The harness may be applied too tightly or may not be modified with the infant's growth, thus causing downward pressure on the brachial plexus nerves and subsequent neuropathy.

Alternatives to harnessing include surgical and nonsurgical reduction of the hip followed by casting. A hip spica cast is most often used with these infants. **Quality and Safety: Care then includes observance for poor pedal pulses, decreased peripheral circulation, pain, skin excoriation or abrasions, and possible development of respiratory infections resulting from decreased mobility.** An adjustment in car seats is required with the harness, and any casting and parental education should be documented prior to discharge of the infant or a specialized car seat may be needed for safe transport of the infant.

HOSPITAL-ACQUIRED POSITIONAL DEFORMITIES: SUPPORTING THE MUSCULOSKELETAL SYSTEM OF THE PREMATURE INFANT IN THE NEONATAL INTENSIVE CARE UNIT

Infants born early are often at a motoric disadvantage. According to Celik, Elbasan, Gucuyener, Kayihan, and Huri (2018), "Disorders in the processing of the signals coming from the proximal sensory systems (vestibular, proprioceptive, tactile) lead to problems in the production of an adaptive response, the development of postural control and movement coordination, and the motor development and the arrangement of the awake-orientation status—all of which affect the development of play, social participation, education, and self-care occupations" (p. 2). Regarding musculoskeletal implications, Sweeney and Gutierrez (2002) state that "alignment and shaping of the musculoskeletal system occur during each body position that infants experience while in neonatal intensive care. Neonatal nurses and physical therapists can play a major role in designing, modeling, and teaching positioning strategies that promote skeletal integrity, postural control, and sensorimotor organization" (p. 58). They continue, describing positioning procedures used by neonatal intensive care unit (NICU)-based healthcare professionals to prevent extremity malalignment, skull deformities, and motor delays.

Infants admitted to the NICU are typically premature and/or medically fragile; therefore, they often demonstrate signs of motoric instability during their hospital stay. Motoric *stability* is indicated by consistent muscle tone appropriate for postconceptual age; controlled activity, including smooth movement of extremities and head; smooth postural changes; demonstration of bright-eyed alertness and visual attention; and attempts to self-regulate through foot clasp (bringing feet together), grasping, bracing, holding on, hand to head or mouth activity, trunk tucking, or sucking. *Instability* is demonstrated through tremors, twitches, startles, coughs, sneezes, yawns, sighs, seizures, flaccidity, hyper/hypotonicity, hyperflexions, frantic activity, fluctuating tone, or eye floating (disorganized eye movements).

Both medical and familial caregivers can support infant musculoskeletal development through recognition of the signs and symptoms of instability and through the use of the following interactions to promote motoric stability: (1) containing the infant's extremities using hands, blankets, positioning aids, and so forth, to promote gentle flexion of the trunk and all extremities; (2) positioning infant with extremities flexed toward midline and hands on face or head; (3) moving the infant slowly to encourage organized position changes; (4) keeping the infant in contact with the bed during movement if possible; (5) allowing opportunities for the infant to use hands and feet to push against surfaces, grasp objects, clasp hands together, and suck; (6) varying infant positions; (7) lifting infant in prone or side lying (as opposed to supine) to promote fetal tuck and calm; (8) providing daily opportunities for tummy time as medically appropriate; (9) performing swaddled bathing; and (10) referring to occupational and physical therapy for specialized evaluation and treatment recommendations.

CRANIOSYNOSTOSIS

The bones that constitute the skull are joined with fibrous joints. These joints are lined with a thin layer of fibrous tissue. Separation of these joints allows for remodeling of the skull at the time of delivery and for rapid growth of the head during the early developmental years. The skull consists of five main sutures: coronal, lambdoidal, squamosal, sagittal, and metopic. The signal for closure of these sutures remains unclear but is believed to be secondary to multiple factors. The various sutures of the skull begin to close clinically in the first year of life, and the process continues into childhood. Complete ossification of these sutures is anticipated in the second or third decade of life. Figures 14.6 and 14.7 illustrate the newborn's cranial sutures.

Premature closure of any suture in the skull results in a clinical condition called *craniosynostosis*. The early closure of a cranial suture typically starts at one point and progresses along the suture line. Premature closure may occur prenatally or postnatally. Only one suture may be prematurely fused, or multiple sutures may be involved. Simple craniosynostosis, which involves one suture, generally occurs as an isolated defect. Complex craniosynostosis describes the premature closure of two or more sutures. This is usually associated with a genetic syndrome such as Apert syndrome or Crouzon syndrome.

Pathology and Clinical Characteristics

Clinical characteristics depend on which suture is affected. The closure of one suture does not allow growth in that area, but generally increases growth in the other areas of the skull. The sagittal suture is the most commonly affected suture. When this suture is involved, the head presents as dolichocephalic, with a long and narrow appearance of the skull and increased length from front to back. Bossing of the frontal and occipital regions is also seen. The coronal suture is the second most common suture involved in premature closure. Bilateral closure of the coronal suture leads to the clinical appearance of a skull that is wide from side to side, but short from front to back (also termed *brachycephaly*). Unilateral

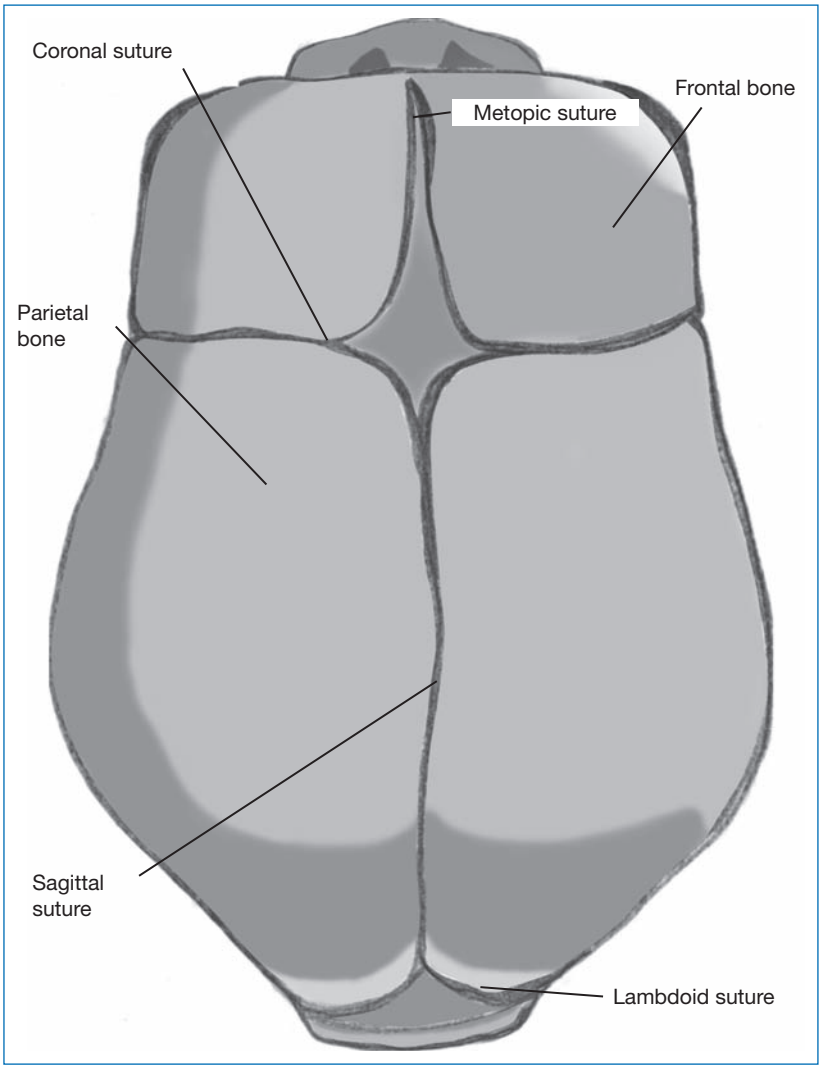

FIGURE 14.6 Superior view of neonatal cranial sutures.

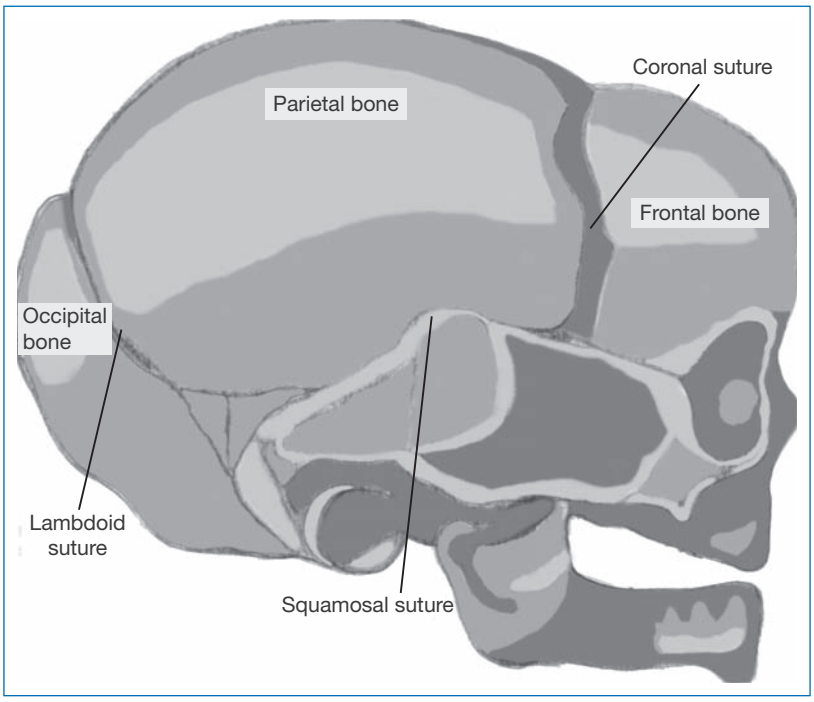

FIGURE 14.7 Lateral view of neonatal cranial sutures.

closure of a coronal suture results in plagiocephaly, or twisted skull, with prominence of the forehead on the unaffected side, as the skull grows in this direction. The forehead is flattened and the eyebrow is raised on the affected side. Bilateral lambdoidal craniosynostosis could be identified with a flattened occipital region, whereas unilateral lambdoidal craniosynostosis has a flattened area on one side of the occiput and appears asymmetrical when compared with the other side. Long-term supine positioning of the infant can also produce this appearance.

Positional asymmetric skull appearance, not related to abnormal suture closure, may be seen in infants with a neuromuscular defect that will not allow the child to move his head from side to side spontaneously. Congenital torticollis can result in an asymmetrically flat occipital region as the infant tilts the head toward the affected side. Isolated metopic craniosynostosis will produce a deformity with a narrow, protruding forehead. Facial development of the skull is affected, and orbital hypotelorism is also noted with this defect.

Diagnosis and Management

Diagnosis is preceded by suspicion of the abnormal physical appearance of the skull, by plagiocephalometry, or by anthropometric measurements with a caliper (Siegenthaler, 2015). There is persistent or progressive abnormal skull growth, often with the head circumference intact for age. Craniosynostosis is usually confirmed with a computed tomography (CT) scan of the skull, with three-dimensional CT required for more detailed preoperative examination. Surgery is required to correct this defect. This will take place in a specialized pediatric hospital with a multidisciplinary team of providers. The complexity of the procedure increases with the number of sutures involved and the cranial remodeling at the time of surgery. The type of repair is dependent on the suture(s) involved. Surgery generally takes place in early infancy (3–9 months of age). The goal is to achieve early correction of the synostosis and avoid extreme cranial deformities as the skull grows rapidly in the first year of life. In recent years, endoscopic procedures have shown good results in reducing the excessive blood loss and extended hospital stays that were previously associated with repair of craniosynostosis.

CONGENITAL MUSCULAR TORTICOLLIS

Congenital muscular torticollis, with an incidence of 0.4% in all live births, is a rare musculoskeletal deformity with unknown pathogenesis. It is known to be primarily a disorder of the sternocleidomastoid muscle.

Pathophysiology

Several theories exist as to the cause of congenital torticollis, including genetics, abnormal uterine positioning, neurogenic disorders, and ischemic injury to the sternocleidomastoid muscle. Whatever the cause, this pathologic disorder consists of a fibrous contraction of the sternocleidomastoid muscle. Typically, the ipsilateral trapezius muscle is atrophied.

Diagnosis

Congenital torticollis can present within the neonatal period. Presentation may include a 1 to 3 cm hard, palpable mass in the neck on the affected side accompanied by an abnormal positioning of the head. Infants with congenital torticollis tilt the head to the affected side, and the chin is pointed upward in the opposite direction. Facial asymmetry may be a later sign. The face and skull on the affected side appear smaller.

In children with untreated congenital torticollis or in cases with torticollis unresponsive to therapy, the shoulder on the affected side is raised to compensate for the abnormal head positioning. This form of compensation may lead to cervical and lumbar scoliosis as well as chronic back pain.

Collaborative Management

Traditionally, occupational and/or physical therapy for congenital torticollis is instituted immediately. Because congenital torticollis may resolve naturally within the first year of life, surgery is typically delayed, pending results of therapy.

Severe fibrosis of the sternocleidomastoid muscle may require surgery (Nilesh & Mukherji, 2013). In one study, however, 98% of infants diagnosed with torticollis responded to physical therapy. Duration of therapy was dependent on severity of the muscular fibrosis (Y. T. Lee et al., 2011).

Occupational therapists, physical therapists, and orthopedic surgeons should be consulted to assist in the management and subsequent follow-up of these infants. Family members should be provided with a functional home exercise program and counseled regarding the possibility of a neck brace to be postoperatively worn by the infant. It is usually the nurse's responsibility to coordinate outpatient consultations and to prepare the family with discharge instructions. In addition, the nurse must determine whether the family lives in an area accessible to follow-up care. If not, a referral to social services, IDEA Part-C Early Intervention services, or financial counseling may be needed so the family can participate in follow-up.

SKELETAL DYSPLASIA

Skeletal dysplasia is a term used to identify a group of clinical disorders that involve abnormal endochondral ossification. It includes achondroplasia, hypochondroplasia, and thanatophoric dysplasia, all of which present with a short-limbed skeletal dysplasia at varying ages of development.

Achondroplasia

Although the word *achondroplasia* was once used to describe any form of dwarfism, it is now recognized as one distinct type of dwarfism having characteristic features. Achondroplasia has an autosomal dominant pattern of inheritance (Wilkin et al., 1998) and is the most common nonlethal skeletal dysplasia. Most cases occur by spontaneous mutation, so many of these children have parents of typical stature. A mutation of the gene encoding fibroblast growth factor receptor-3 (FGFR3) has been implicated in this disorder. In achondroplasia, the infant's body has trouble converting cartilage to bone (ossification). The incidence of achondroplasia has varied in the past as a result of multiple forms of skeletal dysplasia diagnosed as achondroplasia. The current incidence is 1 in 15,000 to 40,000 live births. One risk factor for spontaneous mutation that involves achondroplasia appears to be advanced paternal age.

Infants with achondroplasia can be identified at birth with a rhizomelic shortening of the extremities. In other words, when the arms are viewed, the upper arm (humerus bone) will appear more severely shortened compared with the lower arm (radius and ulnar bones). The same holds for the lower extremities, where the thigh (femur) will appear more severely shortened than the lower leg (tibia and fibular bones). The infant who is affected with achondroplasia also presents with a disproportionately large head with frontal bossing and depressed nasal bridge. The hands are small with a trident configuration that describes the appearance of the fingers and an increased spacing between the long and ring fingers (Horton & Hecht, 2011). Identification of mild hypotonia and limitation of elbow extension with laxity in most other joints are also noted.

These neuromuscular and skeletal anomalies—including mild hypotonia, rhizomelia, joint laxity, and reduced elbow extension—can produce a delay in gross motor milestones but generally progress toward age-appropriate skill over the first few years of life. Commonly associated health problems also include apnea, recurrent ear infections, and obesity. Central intelligence is normal in most cases.

Hypochondroplasia

Hypochondroplasia is similar to achondroplasia but considered milder. It may be rarely noted at birth, as the length of the infant is often age appropriate. The short stature becomes clinically apparent around 24 months of age. This condition is rarely diagnosed in the neonatal period but may present with macrocephaly. Children and adults experience some of the similar orthopedic complications as the individual with achondroplasia. Some of these include joint and lower back pain, limited range of motion at the elbows, and bowing of the lower extremities.

Thanatophoric Dysplasia

Thanatophoric dysplasia is the third in this series of common skeletal dysplasias. The name of this disorder is derived from the Greek word *thanatos*, meaning *death bearing*. It is a lethal defect and is often compared to OI, type II, in terms of its clinical scenario after birth. Death usually occurs within a few hours or days secondary to respiratory failure from severe pulmonary hypoplasia. The clinical presentation of thanatophoric dysplasia describes a fetal environment of reduced fetal movements and polyhydramnios. Hypotonia in the neonate with macrocephaly, often presenting as a cloverleaf-shaped skull, is believed to be secondary to early fusion of the coronal and lambdoidal sutures. The limbs are short and bowed with severe brachydactyly or short digits. The thorax is very narrow and short, reminding the clinician of the abnormal pulmonary development and severe pulmonary hypoplasia. The abdomen has a protuberant appearance (Figures 14.8 and 14.9). Almost all cases of thanatophoric dysplasia result from a new genetic mutation, with a low risk of recurrence in subsequent pregnancies. As with other skeletal dysplasias, there is a defect in the *FGFR3* gene (Miller, Blaser, Shannon, & Widjaja, 2009).

Differential Diagnosis

The differential diagnosis of a neonate with shortened stature includes achondroplasia, OI type II, thanatophoric dwarfism, asphyxiating thoracic dysplasia, lethal short limb–polydactyly syndromes, and achondrogenesis. In achondroplasia, the child has markedly shortened limbs and often bowing of the lower limbs, but radiographic studies do not show evidence of multiple fractures and long-bone crumbling as seen in OI type II. Thanatophoric dwarfism and achondrogenesis, both typically fatal in the neonatal period, are characterized by an extremely narrow chest and marked defective ossification, respectively (Shirley & Ain, 2009). These disorders may be detected prenatally through ultrasound identification of the abnormal skeletal features.

Management

Management of infants with skeletal dysplasias depends on the long-term outcome for the specific type of dysplasia. With nonlethal varieties, complications are primarily neurologic and involve the spinal nerves. Anatomic configuration of the intraspinal canal results in pressure on the cord and spinal nerves. This pressure produces chronic backache and, in the most severe scenario, paraplegia. Referrals to occupational and physical therapists, along with long-term orthopedic follow-up, can reduce some of the complications. **Quality and Safety: If changes in the spinal column do occur, the child is at greatest risk for development of increased respiratory difficulties, mobility problems, daily activity (occupational) challenges, self-concept and self-esteem concerns, physical pain, and central or peripheral nervous system neuropathies.** Other common long-term complications include recurrent otitis media, hearing loss, dental overcrowding, and sleep apnea, which may present in childhood (Sisk, Heatley, Borowski, Leverson, & Pauli, 1999).

Limb-lengthening techniques are sometimes used in management of skeletal dysplasias. This has been done in an attempt to reduce the functional and psychosocial difficulties associated with very short stature. The process of limb lengthening is very arduous and surgically complex, with lengthy rehabilitation periods. Often, the physical outcome does not match the desired result, so the benefit of these procedures remains uncertain (Wright & Irving, 2012).

Because children with achondroplasia have a different appearance than their peers, any exaggeration of the condition can add to a faulty self-concept. As the child grows, continual assessment by healthcare professionals and the parents concerning the personal image that the child is developing is prelude to a positive self-esteem. Positive support of parents during the neonatal period is key.

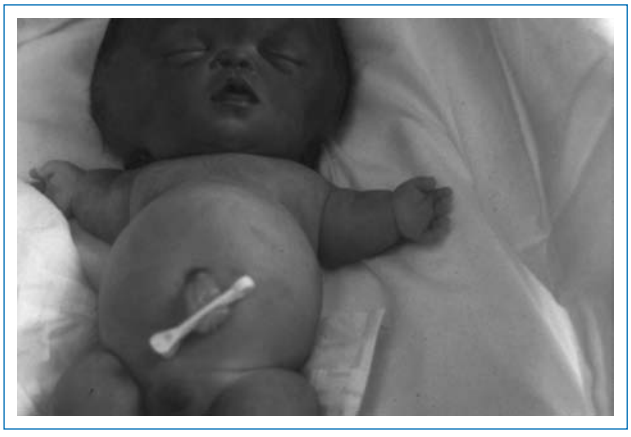

FIGURE 14.8 Thanatophoric dysplasia: narrow thorax and protuberant abdomen.

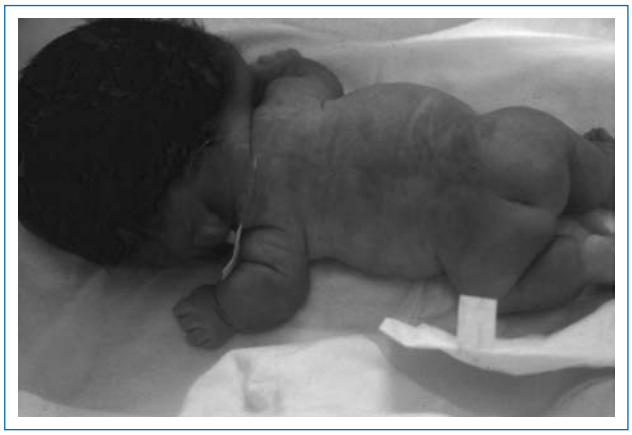

FIGURE 14.9 Thanatophoric dysplasia: shortened lower extremities.

OSTEOGENESIS IMPERFECTA

Osteogenesis imperfecta (OI), sometimes called *brittle bone disease*, is a connective tissue disorder causing bone fragility and deformities (Forlino & Marini, 2016). It is caused by a genetic mutation affecting collagen, the major extracellular protein, wherein children suffer from fractures, osteoporosis, and mineral bone loss. The incidence of this disorder is about 1 per 20,000 births. Collagen is found in bone, sclera, ligaments, skin, and teeth. In this disorder, all of these tissues may be affected (Sillence & Danks, 1978).

The clinical presentation of OI varies greatly, depending on the particular type. There is also a wide range of severity and symptoms within each type. The classification system described by Sillence and Danks (1978) outlines four basic types of OI. Additional types described in the literature do not appear to have defects in the collagen genes.

Types of OI and Clinical Presentation

OI type I has an autosomal dominant inheritance pattern. In general, type I is the mildest type of OI, but the clinical appearance of individuals may range from mild to severe, even within the same family. A small number of patients with this type may present with fractures in the neonatal period. An increased rate of fractures may be seen as the child begins to walk. Persons with this type are generally of typical height and stature. Sclerae are blue, and the teeth are also affected. In adults with type I OI, hearing loss may occur (Bishop, 2010). Premature or accelerated bone loss following menopause is also seen.

OI type II is also referred to as the *lethal perinatal type*. This is an autosomal recessive disorder that generally results in death either in utero or in the perinatal/neonatal period. The likelihood of prenatal diagnosis is increased with type II, due to the multiple fractures and bowing of extremities seen in utero. **Emergency Alert: Death can occur secondary to damage of vital organs (brain, liver, and lungs) that are not protected by the fragile bony structures.** Severe respiratory distress is seen secondary to the narrow and shortened ribcage. Infants with type II OI are small for gestational age with shortened body and legs, with the head appearing large for body size. The extremities tend to be shortened and deformed with multiple fractures. X-rays demonstrate multiple fractures, both old and new. Ribs and smaller bones may also appear thin and difficult to discern on x-ray. The trauma of birth takes a further toll on the appearance of these infants and contributes to the maceration of the head and limbs.

OI type III is a severe form with an autosomal recessive inheritance pattern. This is the most severe type for those surviving the neonatal period. Multiple fractures of the long bones may occur both before and after birth. There is significant deformity of the bones over time, with scoliosis and hearing loss. Sclerae may be blue. Infants with type III may have typical height and weight at birth. This deteriorates over time, with very short stature seen in childhood/adulthood. The severe deformities of the spine and thorax seen in type III can restrict breathing, leading to significant respiratory complications in adulthood. Life expectancy may be shortened due to these problems (Marini, 2011).

OI type IV is similar to type I in that it is an autosomal dominant disorder with variable penetrance. OI type IV resembles type I in terms of presentation. Newborns rarely have identified fractures, but a number of fractures occur as the child begins to ambulate, with increased weight bearing. These infants also present with growth that is average for gestational age. The growth pattern can change as the child matures, secondary to increased bowing of extremities and kyphoscoliosis, with a short stature comparable to typical height at maturity with the milder forms of type I. OI type IV can also progress to a more severe form, depending on the degree of kyphoscoliosis and vertebral compression fractures, often resembling type III. Unlike type III, life span in type IV is not affected.

As stated earlier, additional types of OI have been identified since the original classification system was developed. These are described as types V (moderate in severity), VI (extremely rare), and VII, VIII (white sclerae), which do not have defects in the collagen genes. The clinical features and management are, however, similar to the other types of OI.

Diagnosis

OI may be suspected prenatally if there is a positive family history. Fractures and other deformities of the skeleton may be seen on ultrasound prior to birth at around 20 weeks (Van Dijk & Sillence, 2014). After birth, the diagnostic process is based largely on physical exam findings of fractures and deformities of the extremities. While the preferred method of diagnosis involves molecular genetic testing, a skin biopsy may also be used to provide a definitive diagnosis through examination of collagen (Steiner, Adsit, & Basel, 2013).

Collaborative Management

Quality and Safety: Neonates with OI should be handled very gently to avoid causing new fractures and to reduce the pain of existing injuries. During care, they should be lifted by using the hands to gently support the buttocks and head. These patients should never be lifted by pulling the extremities, or with hands under the armpits. With diaper changes, it is important to never lift the baby by the ankles, but to move the diaper by lifting the buttocks. When dressing these infants, the caregiver should gently bring the garments over the arms and legs, while avoiding pulling the extremities through the sleeves and legs of the garments. Simple garments with wide openings for extremities are best. At discharge, a special car bed that allows prone or supine positioning may be required (Osteogenesis Imperfecta Foundation, n.d.).

Feeding ability may be compromised with these infants, due to respiratory compromise and difficulty with positioning and handling. Gentle rubbing should be used for burping to avoid rib fractures. If these infants require prolonged immobilization during healing of fractures, measures to protect the skin and facilitate frequent repositioning may be used, such as gel pads or foam wedges. **Quality and Safety: Pain management is also an important part of the care plan when fractures are present.** IV medications or oral sucrose may be used, as well as other nursing measures to improve comfort and positioning (McLean, 2004). Referrals to occupational therapy, physical therapy, and palliative care may be indicated.

The long-term medical management of patients with OI is focused on avoiding fractures and correcting deformities of bones while maintaining maximal mobility and physical function. Intravenous bisphosphonates have shown some benefit by improving bone volume, though this does not change the essential defect of collagen (Monti et al., 2010). Growth hormone has also been used with the milder types of OI.

THROMBOCYTOPENIA-ABSENT RADIUS SYNDROME

Thrombocytopenia-absent radius (TAR) syndrome is characterized by the bilateral absence of radii and severe thrombocytopenia in the neonatal period. Hypoplasia or absence of the ulna may also be seen. The thumbs are always present in this syndrome (Scott & Montgomery, 2011). Congenital heart defects and renal anomalies

occur in a significant percentage of these patients. Skeletal anomalies of the lower limbs may also be present, although this is highly variable.

Pathology

The inheritance pattern is uncertain in this disorder, although a microdeletion on chromosome 1 is part of the genetic signature. The greatest pathology occurs in the neonatal period and correlates to the severity of thrombocytopenia, which can lead to intracranial and gastrointestinal hemorrhages (Sola, Del Vecchio, & Rimsza, 2000). The thrombocytopenia is quite significant in many patients, with counts as low as 10,000. Hematologic complications improve with age, hence the reduced mortality and morbidity associated with this syndrome after the first year of life. Platelet counts are generally normal by childhood. If no significant intracranial hemorrhage occurs in the neonatal period, intelligence is expected to be typical for age.

Complications occurring from atypical hand and arm development may be encountered as the child matures. These include fine and gross motor developmental delays. Many children who are affected with this syndrome require some type of adaptive device, or they may learn to compensate with their existing limbs. Referrals to occupational and physical therapy are indicated for specialized assessment and treatment.

Management

The primary management in the newborn period centers on the platelet levels. Because of increased risk of bleeding, platelet transfusions may be required. In addition, handling and phlebotomy via heel sticks should be kept to a minimum to reduce bruising. Cow's milk allergy is seen in many patients with TAR syndrome. The introduction of cow's milk may lead to worsening of thrombocytopenia, and this factor should be considered in management (Toriello, 2011).

SUMMARY

The human body is active, responsive, and constantly moving. The development of its functional motor skills is dependent upon the development of the musculoskeletal system. Although the majority of musculoskeletal defects or disorders in the newborn are nonlethal, they may become the focus of the parents' attention. An understanding of the development of the musculoskeletal system and the pathology for various defects can assist the clinician in teaching and supporting the family and the infant. In addition, recognizing subtle abnormalities can prompt the clinician to evaluate for additional, associated defects that could have serious genetic implications. This chapter helps identify the epidemiological and clinical aspects of infant musculoskeletal conditions in order to improve clinician understanding of the defect and to provide guidelines for management based on pathology, complications, and prognosis. Of equal importance, however, is the awareness that musculoskeletal development is best supported in a family-centered environment and in collaboration with parents eager to maximize their child's potential.

CASE STUDY

■ **Identification of the Problem.** Female infant born at term gestation is noted on initial physical exam to have abnormalities of the upper extremities.

■ **Assessment: History and Physical Examination.** The infant was born by vaginal delivery at 37 weeks gestation to a 16-year-old Caucasian female, G1 P0. The mother received late and limited prenatal care, with the pregnancy remaining unacknowledged until the third trimester secondary to young maternal age. Delivery was uncomplicated. The 1-minute Apgar score was 9, and the infant did not require resuscitation or other special care at delivery. The birth weight was 2,850 g. Infant was noted on general inspection to have abnormalities of the upper extremities.

Physical exam on admission to the transition nursery:

- GENERAL: pink, well-developed female infant, vital signs in the normal range, oxygen saturation was 98% on room air
- Head, ears, eyes, nose and throat (HEENT): normocephalic, anterior fontanelle open and flat, eyes normal, ears normally formed, nares patent, palate intact
- LUNGS: bilateral breath sounds clear and equal, good respiratory effort
- Cardiovascular (CV): RRR, soft murmur, good peripheral perfusion, femoral and pedal pulses palpable
- Abdomen (ABD): soft, active bowel sounds, no organomegaly or masses, three-vessel cord
- Genitourinary (GU): normal term female features, patent anus
- Neurologic (NEURO): appropriate tone for gestational age, active and responsive
- NECK: full range of motion, no masses
- SPINE: intact
- EXTREMITIES: bilateral malformed upper extremities with thumbs present, lower extremities appropriate for age
- SKIN: pink, scattered petechiae over the trunk and face

■ **Suspected Diagnosis.** In this patient, the physical exam findings led to a strong suspicion of TAR syndrome. Immediate evaluation would be indicated to assess platelet count, which can be very low with risk of hemorrhage. Cranial ultrasound should be done to rule out intracranial bleeding. Evaluation of the skeletal structure of the upper extremities would also needed. Echocardiogram should be performed to rule out cardiac defects, which are present in a large percentage of patients with this disorder.

■ **Diagnostic Tests**

1. Complete blood count with differential: WBC 12.7, hematocrit 39%, platelet count 28,000/mm^3
2. X-rays of upper extremities: bilateral absence of radii, with hypoplasia of the ulnae bilaterally; the humeri were present and normal bilaterally; x-rays of lower extremities revealed no abnormalities
3. Echocardiogram: patent ductus arteriosus, no significant structural abnormalities
4. Cranial ultrasound: no evidence of intracranial hemorrhage

■ **Development of Management Plan**

- Platelet transfusion
- Gentle handling of infant to avoid bruising and bleeding
- Close monitoring of the platelet count

■ **Implementation of Management Plan.** The infant was transferred to NICU to obtain a peripheral IV and to have the necessary studies completed. The platelet count was repeated 12 hours after the transfusion with a value of 49,000/mm^3. The infant received an additional transfusion of platelets with improvement to 72,000/mm^3. The infant remained hospitalized for an additional week while receiving ad lib breastfeedings. She remained stable. Repeat cranial ultrasound at 7 days of age was again normal.

The infant was discharged home at 10 days of age with platelet count 80,000/mm^3. She returned to the newborn outpatient clinic 3 days later with platelet count 43,000/mm^3. An additional platelet transfusion was given in the outpatient clinic with no complications. The platelet count on a follow-up visit the next day was 85,000/mm^3. The infant continued to receive periodic follow-up visits for complete blood count monitoring over the next 3 months. She required no further platelet transfusion.

■ **Outcome.** Infant was seen at 6 months of age in the newborn follow-up clinic with typical growth and development. Platelet count was normal.

EVIDENCE-BASED PRACTICE BOX

Osteogenesis imperfecta (OI), often called *brittle bone disease*, is a condition caused by a genetic mutation affecting collagen. The complications of OI stem primarily from bone fractures. The treatment of these patients focuses chiefly on preventing fractures, therefore minimizing pain and improving long-term mobility and function. A number of research studies have investigated the use of bisphosphonates to reduce fracture rates in patients with OI. Biphosphonates act by decreasing the activity of osteoclasts, therefore reducing the rate of bone resorption. These drugs are used successfully in adults with osteoporosis to improve bone strength and density.

A review by Bishop (2010) examined the early use of intravenous pamidronate in neonates in the first year of life. The drug was given on a cyclical basis at varying intervals. A reduced rate of fractures was seen in these infants, as well as improved growth. No severe side effects were documented. There are concerns regarding the difficulty of maintaining reliable central venous access in a small infant. Also, the long-term effects of this therapy remain unknown. It should be noted that the drug does not change the process of abnormal collagen formation.

Growth hormone, which is known to stimulate bone growth and collagen synthesis, has also been examined as a potential treatment for OI. A review by Monti et al. (2010) examined the available information. Data from limited studies suggested that growth hormone could improve growth and exert a beneficial effect on muscle mass and strength, therefore improving capacity for exercise; no increased rate of fractures was noted. This increase in physical activity in OI patients may improve skeletal health and overall physical well-being. Growth hormone is considered a promising therapy in patients with moderate forms of OI. Patients with the more severe types of the disorder did not see a benefit.

Research in the arena of genetics is very promising. Investigators hope to identify more specific causative factors at the molecular level, as well as to explore the possibility of manipulating the disorder's genetic expression. Bone marrow transplant is also being examined as a potential treatment. Limited data suggest that bone marrow transplant can be used to introduce stem cells into the body that can produce normal bone. These modalities remain in early stages of development.

References

Bishop, N. (2010). Characterising and treating osteogenesis imperfecta. *Early Human Development, 86*, 743–746. doi:10.1016/j.earlhumdev.2010.08.002

Monti, E., Mottes, M., Fraschini, P., Brunelli, P., Forlino, A., Venturi, G., . . . Antoniazzi, F. (2010). Current and emerging treatments for the management of osteogenesis imperfecta. *Therapeutics and Clinical Risk Management, 6*, 367–381. doi:10.2147/tcrm.s5932

ONLINE RESOURCES

Ebraheim, N. [nabil ebraheim]. (2014, March 25). *Barlow & Ortolani test, congenital hip dislocation–Everything you need to know–Dr. Nabil Ebraheim* [Video file]. Retrieved from https://www.youtube.com/watch?v=imhI6PLtGLc

Consolini, D. M. (2016). Evaluation and care of the normal neonate. In R. S. Porter (Ed.), *Merck manual: Professional version* [Online]. Retrieved from http://www.merckmanuals.com/professional/pediatrics/approach_to_the_care_of_normal_infants_and_children/evaluation_and_care_of_the_normal_neonate.html

REFERENCES

Alexander, R., Boehme, R., & Cupps, B. (1993). *Normal development of functional motor skills: The first year of life*. Tucson, AZ: Therapy Skill Builders.

Alnamshan, M. K., Jawadi, A. H., Alshoaibi, Y. A., & Moukaddem, A. (2018). Outcome of delayed surgery in developmental hip dysplasia in a tertiary care setting. *The Egyptian Journal of Hospital Medicine, 73*(4), 6446–6451. doi:10.12816/ejhm.2018.15109

Baraitser, M., & Winter, R. M. (1996). *Color atlas of congenital malformation syndromes*. St. Louis, MO: Mosby.

Barlow, T. G. (1962). Early diagnosis and treatment of congenital dislocation of the hip. *Journal of Bone and Joint Surgery, 44B*, 292–301. doi:10.1302/0301-620x.44b2.292

Betts, J. G., Desaix, P., Johnson, E., Johnson, J. E., Korol, O., Kruse, D., . . . Young, K. A. (2013). Anatomy & physiology (pp. 345–349). Houston, TX: Rice University. Retrieved from https://opentextbc.ca/anatomyandphysiology/chapter/9-5-types-of-body-movements

Bialocerkowski, A. E., & Vladusic, S. L. (2008). Prevalence, risk factors, and natural history of positional plagiocephaly: A systematic review. *Developmental Medicine and Child Neurology, 50*(8), 577–586. doi:10.1111/j.1469-8749.2008.03029.x

Bianchi, D. W., & Van Marter, L. J. (1994). An approach to ventilator-dependent neonates with arthrogryposis. *Pediatrics, 94*(5), 682–686. Retrieved from https://pediatrics.aappublications.org/content/94/5/682..info

Bishop, N. (2010). Characterising and treating osteogenesis imperfecta. *Early Human Development, 86*, 743–746. doi:10.1016/j.earlhumdev.2010.08.002

Byrne, E., & Garber, J. (2013). Physical therapy intervention in the neonatal intensive care unit. *Physical and Occupational Therapy in Pediatrics, 33*(1), 75–110. doi:10.3109/01942638.2012.750870

Celik, H. I., Elbasan, B., Gucuyener, K., Kayihan, H., & Huri, M. (2018). Investigation of the relationship between sensory processing and motor development in preterm infants. *American Journal of Occupational Therapy, 72*, 7201195020p1–7201195020p7. doi:10.5014/ajot.2018.026260

Chaturvedi, A. P., Chaturvedi, A. B., Stanescu, A. L., Blickman, J. G., & Meyers, S. P. (2018). Mechanical birth-related trauma to the neonate: An imaging perspective. *Insights Into Imaging, 9*(1), 103–118. doi:10.1007/s13244-017-0586-x

Forlino, A., & Marini, J. C. (2016). Osteogenesis imperfecta. *The Lancet, 387*(10028), 1657–1671. doi:10.1016/S0140-6736(15)00728-X

Horton, W. A., & Hecht, J. T. (2011). Disorders involving transmembrane receptors. In R. M. Kliegman, B. F. Stanton, J. W. St Geme III, N. F. Schor, & R. E. Behrman (Eds.), *Nelson textbook of pediatrics* (19th ed., pp. 2428–2429). Philadelphia, PA: Elsevier Saunders.

Huelke, D. F. (1998). An overview of the anatomical considerations of infants and children in the adult world of automobile safety design. *Association for the Advancement of Automotive Science, 42*, 93–113. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3400202

Hunter, J., Lee, A., & Altimier, L. (2015). Neonatal intensive care unit. In J. Case-Smith & J. C. O'Brien (Eds.), *Occupational therapy for children and adolescents* (7th ed., pp. 595–635). St. Louis, MO: Elsevier.

Kimber, E. (2015). AMC: Amyoplasia and distal arthrogryposis. *Journal of Children's Orthopaedics, 9*(6), 427–432. doi:10.1007/s11832-015-0689-1

Lakhani, S., Doan, R., Almureikhi, M., Partlow, J. N., Al Saffar, M., Elsaid, M. F., . . . Ben-Omran, T. (2017). Identification of a novel *CNTNAP!* Mutation causing arthrogryposis multiplex congenita with cerebral and cerebellar atrophy. *European Journal of Medical Genetics, 60*(5), 245–249. doi:10.1016/j.ejmg.2017.02.006

Lee, S. H., Lee, M., Kim, M., Son, G., & Namgung, K. (2011). Fetal MR imaging of constriction band syndrome involving the skull and brain. *Journal of Computer Assisted Tomography, 35*(6), 685–687. doi:10.1097/rct.0b013e31823489ae

Lee, Y. T., Yoon, K., Kim, Y. B., Chung, P. W., Hwang, J. H., Park, Y. S., . . . Han, B. H. (2011). Clinical features and outcome of physiotherapy in early presenting congenital muscular torticollis with severe fibrosis on ultrasonography. A prospective study. *Journal of Pediatric Surgery, 46*(8), 1526–1531. doi:10.1016/j.jpedsurg.2011.02.040

Lippert, L. S. (2011). *Clinical kinesiology and anatomy* (5th ed.). Philadelphia, PA: F. A. Davis.

Liu, R.W., & G.H.Thompson (2019). Musculosketal disorders in neonates. In R. J. Martin, A. A. Fanaroff, & M. C. Walsh (Eds.) *Fanaroff & Martin's neonatal-perinatal medicine* E-Book (11th ed., pp. 2195–2204). Philadelphia, PA: Elsevier.

Marini, J. C. (2011). Osteogenesis imperfecta. In R. M. Kliegman, B. F. Stanton, J. W. St Geme III, N. F. Schor, & R. E. Behrman (Eds.), *Nelson textbook of pediatrics* (19th ed., pp. 2437–2439). Philadelphia, PA: Elsevier Saunders.

McLean, K. R. (2004). Osteogenesis imperfecta. *Neonatal Network, 23*(2), 7–14. doi:10.1891/0730-0832.23.2.7

Miller, E., Blaser, S., Shannon, P., & Widjaja, E. (2009). Brain and bone abnormalities of thanatophoric dwarfism. *American Journal of Roentgenology, 192*(1), 48–51. doi:10.2214/ajr.08.1524

Monti, E., Mottes, M., Fraschini, P., Brunelli, P., Forlino, A., Venturi, G., . . . Antoniazzi, F. (2010). Current and emerging treatments for the management of osteogenesis imperfecta. *Therapeutics and Clinical Risk Management, 6*, 367–381. doi:10.2147/tcrm.s5932

Morey, S. S. (2001). AAP develops guidelines for early detection of dislocated hips. *American Family Physician, 63*, 565–566. Retrieved from https://www.aafp.org/afp/2001/0201/p565.html

Mostert, A. K., Tulp, N. J., & Castelein, R. M. (2000). Results of Pavlik harness treatment for neonatal hip dislocation to Graf's sonographic classification. *Journal of Pediatric Orthopedics, 20*, 306–310. doi:10.1097/01241398-200005000-00007

National Cancer Institute. (n.d.). Anatomical terminology. Retrieved from https://training.seer.cancer.gov/anatomy/body/terminology.html

Nilesh, K., & Mukherji, S. (2013). Congenital muscular torticollis. *Annals of Maxillofacial Surgery, 3*(2), 198–200. doi:10.4103/2231-0746.119222

O'Berry, P., Brown, M., Phillips, L., & Evans, S. H. (2017). Obstetrical brachial plexus palsy. *Current Problems in Pediatric and Adolescent Care, 47*(7), 151–155. doi:10.1016/j.cppeds.2017.06.003

O'Brien, J. (2015). Application of motor control/motor learning to practice. In J. Case-Smith & J. Clifford O'Brien (Eds.), *Occupational therapy for children and adolescents* (7th ed., pp. 193–219). St. Louis, MO: Elsevier.

O'Flaherty, P. (2001). Arthrogryposis multiplex congenita. *Neonatal Network, 20*(4), 13–20. doi:10.1891/0730-0832.20.4.13

Ortolani, M. (1976). Congenital hip dysplasia in the light of early and very early diagnosis. *Clinical Orthopedics and Related Research, 119*, 6–10.

Osteogenesis Imperfecta Foundation. (n.d.). Neonatal and nursery care. Retrieved from http://www.oif.org/site/DocServer/Neonatal_and_Nursery_Care__Pdf_for_page_12.0_.pdf?docID=7362

Scott, J. P., & Montgomery, R. R. (2011). Neonatal thrombocytopenia. In R. M. Kliegman, B. F. Stanton, J. W. St Geme III, N. F. Schor, & R. E. Behrman (Eds.), *Nelson textbook of pediatrics* (19th ed., pp. 1714–1722). Philadelphia, PA: Elsevier Saunders.

Shirley, E. D., & Ain, M. C. (2009). Achondroplasia: Manifestations and treatment. *Journal of the American Academy of Orthopedic Surgeons, 17*(4), 231–241.

Shorter, D., Hong, T., & Osborn, D. A. (2011). Screening programmes for developmental dysplasia of the hip in newborn infants. *Cochrane Database of Systematic Reviews*, (9), CD004595. doi:10.1002/14651858.cd004595.pub2

Siegenthaler, M. H. (2015). Methods to diagnose, classify, and monitor infantile deformational plagiocephaly and brachycephaly: A narrative review. *Journal of Chiropractic Medicine, 14*(3), 191–204. doi:10.1016/j.jcm.2015.05.003

Sillence, D., & Danks, D. (1978). The differentiation of genetically distinct varieties of osteogenesis imperfecta in the newborn period. *Clinical Research, 26*, 178A.

Sisk, E. A., Heatley, D. G., Borowski, B. J., Leverson, G. E., & Pauli, R. M. (1999). Obstructive sleep apnea in children with achondroplasia: Surgical and anesthetic considerations. *Otolaryngology-Head and Neck Surgery, 120*, 248–254. doi:10.1016/s0194-5998(99)70414-6

Smythe, T., Mudariki, D., Kuper, H., Lavy, C., & Foster, A. (2017). Assessment of success of the Ponseti method of clubfoot management in sub Saharan Africa: A systematic review. *BMC Musculoskeletal Disorders, 18*, 1–10. doi:10.1186/s12891-017-1814-8

Sola, M. C., Del Vecchio, A., & Rimsza, L. M. (2000). Evaluation and treatment of thrombocytopenia in the neonatal intensive care unit. *Clinics in Perinatology, 27*(3), 655–679. doi:10.1016/s0095-5108(05)70044-0

Steiner, R. D., Adsit, J., & Basel, D. (2013, February 14). *COL1A1/2*-related osteogenesis imperfecta. In M. P. Adam, H. H. Ardinger, R. A. Pagon, & S. E. Wallace (Eds.), *GeneReviews* [Internet]. Seattle: University of Washington, Seattle. Retrieved from http://www.ncbi.nlm.nih.gov/books/NBK1295

Stelzeneder, D., Mamisch, T. C., Kress, I., Domayer, S. E., Werlen, S., Bixby, S. D., . . . Kim, Y. J. (2012). Patterns of joint damage seen on MRI in early hip osteoarthritis due to structural hip deformities. *Osteoarthritis and Cartilage, 20*(7), 661–669. doi:10.1016/j.joca.2012.03.014

Strauss, A., Hasbargen, U., Paek, B., Bauerfeind, I., & Hepp, H. (2000). Intra-uterine fetal demise caused by amniotic band syndrome after standard amniocentesis. *Fetal Diagnosis and Therapy, 15*(1), 4–7.

Sweeney, J. K., & Gutierrez, T. (2002). Musculoskeletal implications of preterm infant positioning in the NICU. *Journal of Perinatal and Neonatal Nursing, 16*(l), 58–70. doi:10.1097/00005237-200206000-00007

Toriello, H. V. (2011). Thrombocytopenia-absent radius syndrome. *Seminars in Thrombosis and Hemostasis, 37*(6), 707–712. doi:10.1055/s-0031-1291381

Van Dijk, F. S., & Sillence, D. O. (2014). Osteogenesis imperfecta: Clinical diagnosis, nomenclature and severity assessment. *American Journal of Medical Genetics (Part A), 164*(5), 1470–1481. doi:10.1002/ajmg.a.36545

Wilkin, D. J., Szabo, J. K., Cameron, R., Henderson, S., Bellus, G. A., Mack, M. L., . . . Francomano, C. A. (1998). Mutations in fibroblast growth-factor receptor 3 in sporadic cases of achondroplasia occur exclusively on the paternally derived chromosome. *American Journal of Human Genetics, 63*, 711–716. doi:10.1086/302000

Williams, D., Protopapa, E., Stohr, K., Hunter, J. B., & Roposch, A. (2016). The most relevant diagnostic criteria for developmental dysplasia of the hip: A study of British specialists. *BMC Musculoskeletal Disorders, 17*(38), 1–10. doi:10.1186/s12891-016-0867-4

World Health Organization. (2018). *Musculosketal conditions*. Retrieved from http://www.who.int/news-room/fact-sheets/detail/musculoskeletal-conditions

Wright, M. J., & Irving, M. D. (2012). Clinical management of achondroplasia. *Archives of Disease in Childhood, 97*(2), 129–134. doi:10.1136/adc.2010.189092

CHAPTER 15

Neurologic System

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INTRODUCTION

The central nervous system (CNS) is an extraordinarily complex system. Normal function of the CNS is critical to the function of every organ in the body and for the integration of organ systems that coordinate physiologic and neurobehavioral processes. Neurologic dysfunction during the neonatal period can arise from insults that occur before, during, or after birth. Such insults can affect the infant's ability to survive in the perinatal and neonatal periods and have implications for later developmental and cognitive outcomes. Thus, alterations in neurologic function in the neonate have significant immediate and long-term consequences for the infant and family. Early recognition of infants at risk for neurologic dysfunction and prompt implementation of appropriate interventions are crucial for both the survival and reduction in long-term morbidity.

This chapter examines the structural and functional development of the CNS in the embryo, fetus, and neonate and the basis for common congenital and developmental anomalies. Neurologic assessment of the neonate and related diagnostic techniques are also presented, as are selected pathophysiologic problems that affect the central and peripheral nervous systems. The neurologic problems examined include neonatal seizures, intracranial hemorrhage, brain injury in preterm infants, hypoxic-ischemic encephalopathy (HIE), structural alterations, and birth injuries. Figure 15.1 shows the general structure of the newborn brain.

CNS DEVELOPMENT AND STRUCTURAL ABNORMALITIES

Many disorders of the neurologic system are related to defects in the development of the CNS. The development of the CNS can be divided into six stages: (a) neurulation, (b) prosencephalic development, (c) neuronal proliferation, (d) neuronal migration, (e) organization, and (f) myelination. These stages overlap, and development progresses at different rates in various sections of the CNS. Embryologic development of the CNS begins shortly after fertilization, and maturation continues after birth until adulthood. The CNS therefore is one of the earliest systems to begin development and one of the last to reach maturity. The stages of CNS development are summarized in Table 15.1. CNS development is controlled by developmental genes in a complex cascade of signaling molecules, neurotropic growth factors, and vitamins (such as vitamin A and folic acid) mediating gene expression along the anterior–posterior axis of the embryo (Gressens & Hüppi, 2015; Yuskaitis & Pomeroy, 2017).

Neurulation

Neurulation is the process by which the formation of the central neuroaxis, that is, the brain and spinal cord, occurs as a result of inductive events within the dorsal aspect of the embryo (Table 15.1). The inductive events are separated into two stages: primary neurulation, the events related to the formation of the brain and spinal cord excluding the caudal segments of the lumbar region; and secondary neurulation, the events related to caudal neural tube formation (du Plessis & Volpe, 2018).

Primary neurulation occurs during the first 3 to 4 weeks of gestation and involves the formation of the primitive brain and spinal cord except the lower sacral and coccygeal segments. The CNS arises as a thickening of the ectoderm on the dorsal portion of the embryo at about 18 days' gestation. The brain and spinal cord develop from this thickening, which is called the neural plate. The neural plate invaginates, forming the midline neural groove along the dorsal surface of the embryo. The parallel folds of tissue on either side of this groove are called the neural folds. The neural folds eventually form the forebrain, midbrain, hindbrain, and spinal cord. By the end of the third postconceptional week, the neural folds fuse to form the neural tube. The cranial portion of the lumen of the neural tube forms the ventricles; the caudal portion forms the central canal of the spinal cord. The tissues of the neural tube interact with surrounding mesoderm tissues (somites) to stimulate development of the bony structures, the skull and vertebrae, of the CNS (du Plessis & Volpe, 2018; Moore, Persaud, & Torchia, 2015).

In the fusion of the neural folds, some of the neuroectodermal cells on the upper margins are not incorporated into the neural tube. These cells form the neural crest, which lies between the neural tube and the surface ectodermal layer. The neural crest tissue forms the peripheral nervous system, which includes the cranial, spinal, and autonomic system ganglia and nerves, Schwann cells, melanocyte (pigment) cells, meninges, and skeletal and muscular components of the head (du Plessis & Volpe, 2018; Moore et al., 2015).

Closure of the neural tube begins in the occipitocervical region (at the level of the future hindbrain and cervical junction) at about 22 days' gestation (du Plessis & Volpe, 2018). The neural folds do

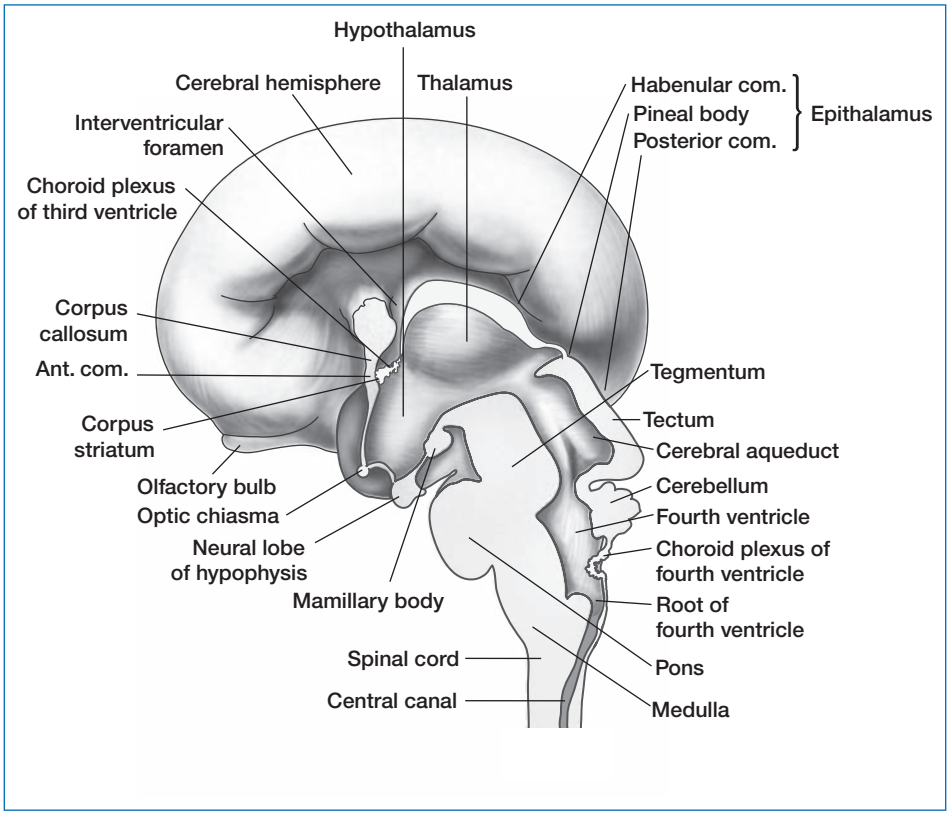

FIGURE 15.1 Cerebral anatomy.

TABLE 15.1

STAGES IN THE DEVELOPMENT OF THE CNS AND RELATED DEVELOPMENTAL DEFECTS

Stage	Peak Period of Occurrence	Examples of Developmental Defects
Primary neurulation	3–4 weeks' gestation	Neural tube defects, anencephaly, encephalocele, spina bifida cystica (meningocele, myelomeningocele, myeloschisis), dermal sinus
Prosencephalic development	2–3 months' gestation	Holoprosencephaly, holotelencephaly
Neuronal proliferation	Cerebrum: 3–4 months' gestation (may continue to term for interneurons) Cerebellum: 2–10 months postnatally	Microcephaly vera, macrencephaly, neurofibromatosis, other neurocutaneous disorders
Neuronal migration	Cerebrum: 3–5 months' gestation (may continue to term for interneurons) Cerebellum: 4–10 months postnatally	Hypoplasia or agenesis of the corpus callosum, schizencephaly, lissencephaly, pachygyria, polymicrogyria
Organization	6 months' gestation—first years postnatal (continues for many years postbirth)	Alterations in brain development secondary to the effects of Down syndrome and trisomy 13, 14, and 15; behavioral alterations; intellectual disabilities
Myelination	8 months' gestation—first years postnatal (continues for many years postbirth)	Brain hypoplasia, neurologic deficits

Sources: Compiled from du Plessis, A. J., & Volpe, J. J. (2018). Neural tube development. In J. J. Volpe, T. E. Inder, B. T. Darras, L. S. de Vries, A. J. du Plessis, J. J. Neil, & J. M. Perlman (Eds.), *Volpe's neurology of the newborn* (6th ed., pp. 3–33). Philadelphia, PA: Elsevier; Huang, S. B., & Doherty, D. (2018). Congenital malformations of the central nervous system. In C. A. Gleason & S. E. Juul (Eds.), *Avery's diseases of the newborn* (10th ed., pp. 857–878). Philadelphia, PA: Elsevier; Gressens, P., & Hüppi, P. S. (2015). Normal and abnormal brain development. In R. J. Martin, A. A. Fanaroff, & M. C. Walsh (Eds.), *Fanaroff and Martin's neonatal-perinatal medicine: Diseases of the fetus and infant* (10th ed., pp. 836–865). Philadelphia, PA: Elsevier Saunders; Yuskaitis, C. J., & Pomeroy, S. L. (2017). Development of the nervous system. In R. A. Polin, S. H. Abman, D. H. Rowitch, W. E. Benitz, & W. W. Fox (Eds.), *Fetal and neonatal physiology* (5th ed., pp. 1294–1313). Philadelphia, PA: Elsevier Saunders.

not fuse simultaneously; fusion proceeds in cephalic and caudal directions from this site. For several days the neural tube is fused toward the central area but is open at both ends. The end areas are known as the rostral (anterior) and the caudal (posterior) neuropores. The cranial end of the neural tube closes at approximately 24 days' gestation. Fusion of the cranial portion contributes to the formation of the forebrain. The caudal neuropore, which is in the future lumbosacral area, closes in a rostrocaudal direction at approximately 26 days' gestation (du Plessis & Volpe, 2018). Once both neuropores are closed, the neural tube is a closed, fluid-filled system that has no further connection to the amniotic cavity unless a defect is present. Alterations in neural tube development and closure give rise to neural tube defects (NTDs). Because differentiation of the surrounding mesodermal tissue (somites) into vertebrae, cranium, and dura depends on interaction with the neural tube, NTDs involve not only the neural elements but also the bony structures and meninges (Blackburn, 2018; du Plessis & Volpe, 2018; Moore et al., 2015).

Secondary neurulation consists of two sequential phases: canalization and regressive differentiation. These phases form the spinal cord of the sacral and coccygeal segments. Canalization begins at 28 to 32 days' gestation and continues through the seventh week of gestation and involves the development of the lower lumbar, sacral, and coccygeal areas from an undifferentiated cell mass at the caudal end of the neural tube. Vacuoles develop that gradually coalesce, enlarge, and contact the caudal end of the neural tube. The second phase, regressive differentiation, begins about the seventh week and continues until sometime after birth. Regressive differentiation is characterized by regression of much of the caudal cell mass, leaving behind the ventriculus terminalis, which is located in the conus medullaris, and the filum terminale (Blackburn, 2018; du Plessis & Volpe, 2018).

Disorders of Neurulation. Congenital anomalies that arise during the period of neurulation result from alterations in neural tube closure, of which 80% occur at either the cranial or caudal end, or alterations in surrounding tissues under development during this period (du Plessis & Volpe, 2018; Moore et al., 2015). Alterations in neurulation are often accompanied by alterations in vertebral, meningeal, vascular, and dermal structures, and include craniorachischisis totalis, anencephaly, encephalocele, spina bifida occulta and cystica (meningocele, myelomeningocele [MMC], and myeloschisis), and Chiari type II malformations (Blackburn, 2018; du Plessis & Volpe, 2018). NTDs are one of the most common CNS malformations. Incidence varies with ethnicity, diet, geographic area, and socioeconomic status; prevalence has decreased with increased folic acid intake by childbearing women (Danzer, Rintoul, & Adzick, 2017).

Disorders of neurulation arise from genetic, nutritional, and/or environmental influences (Blackburn, 2018; du Plessis & Volpe, 2018; Gressens & Hüppi, 2015; Yuskaitis & Pomeroy, 2017). A familial incidence and an increased genetic susceptibility within immediate families is seen. The risk for an NTD increases three- to fivefold for subsequent offspring after one affected child; the risk increases to 10-fold with two or more affected family members (Danzer et al., 2017). In addition, the risk of NTD is greater if the previously affected family member had a lesion at T11 or higher. In the general population, increased risk of NTD is associated with maternal diabetes, maternal obesity, prior miscarriages, maternal folate deficiency, and maternal exposure to drugs such as valproic acid and folic acid antagonists such as trimethoprim and carbamazepine (Au, Ashley-Koch, & Northrup, 2010; Chitayat et al., 2015; du Plessis & Volpe, 2018).

Folic acid supplementation at conception reduces the rate of NTDs (Balashova et al., 2018; Breimer & Nilsson, 2012; Chitayat et al., 2015). Up to 50% to 72% of NTDs may be preventable with adequate folate supplementation (du Plessis & Volpe, 2018). Folate is a cofactor for enzymes needed in DNA and RNA synthesis and is important to a cell's ability to methylate proteins, lipids, and myelin, for cell proliferation and growth, and for the actions of other B vitamins (Balashova, Visina, & Borodinsky, 2018; Czeizel, Dudás, Paput, & Bánhidy, 2011). Women of childbearing age are recommended to consume 0.4 mg of folate daily; for women who previously have had an infant with NTD, the recommendation is 4 to 5 mg daily (American Academy of Pediatrics Committee on Genetics, 1999; Czeizel et al., 2011).

Antenatal screening for NTDs involves maternal serum alpha-fetoprotein screening (MSAFP) and ultrasound examination, or, more commonly, just second trimester ultrasound (American College of Obstetricians and Gynecologists [ACOG], 2017). Analysis of MSAFP is performed between 15 and 20 weeks' gestation, with the optimal time between 16 and 18 weeks' gestation. AFP is a major fetal glycoprotein, similar to the albumin produced in the fetal liver from 6 weeks' gestation; concentrations of AFP peak at 13 to 15 weeks' gestation. Normally, the AFP concentration of the cerebrospinal fluid (CSF) is significantly higher than that of the amniotic fluid; therefore, when CSF leaks into the amniotic fluid, as occurs with an open NTD, the AFP level of the amniotic fluid and maternal serum is elevated. MSAFP is done much less frequently currently due to improvements in ultrasonography and increased use of second trimester fetal anatomic assessment; the detection rate is 96% (ACOG, 2017; Sepulveda et al., 2017). Fetal ultrasound can be used for detection by the end of the first trimester, although the detection rate is lower (ACOG, 2017; Orlandi, Rossi, Perino, Cucinella, & Orlandi, 2016). MRI has also been used to complement use of ultrasound (Cavalheiro, da Costa, Moron, & Leonard, 2017). If MSAFP screening is used, elevated AFP levels are followed up with examination by fetal ultrasound to determine if the elevated AFP levels are the result of open NTD or other causes, such as open abdominal wall defects (gastroschisis and omphalocele), congenital nephrosis, or fetal demise (ACOG, 2017; Sepulveda et al., 2017).

Anencephaly. Anencephaly is associated with failure of the anterior neural tube to fuse in the cranial area. The primary defect may involve failure of normal mesenchyme and cutaneous (i.e., skin, bone, and dorsal coverings) development (du Plessis & Volpe, 2018). Since the advent of antenatal diagnosis and folic acid therapy, the incidence of infants born with anencephaly has markedly declined. Because fusion of the anterior neural tube contributes to the forebrain, anencephalic infants have minimal development of the brain. The brain tissue that does develop is poorly differentiated and becomes necrotic with exposure to amniotic fluid; this results in a mass of vascular tissue with neuronal and glial elements and a choroid plexus marked by partial absence of the skull bones. Anencephaly is thought to occur before about 24 days' gestation, around the period of closure of the rostral neuropore (du Plessis & Volpe, 2018).

Anencephalic infants often have other anomalies. Three-fourths are stillborn; live born infants usually die within the first postnatal month, generally by the end of the first week (du Plessis & Volpe, 2018; Huang & Doherty, 2018). Management of infants with anencephaly is supportive, involving provision of warmth and comfort until the infant dies. Families require emotional support and assistance in coping with their grief over the birth of an infant with a defect and the death of their infant.

Encephalocele. Encephaloceles are "developmental disorders of cranial mesoderm . . . associated with a cystic extracranial extension of meninges, neural tissues and cerebrospinal fluid"

(du Plessis & Volpe, 2018, p. 9). Thus, encephalocele is thought to be a postneurulation disorder involving a skull defect through which neural tissue protrudes (Huang & Doherty, 2018). Although this defect can occur in any region, approximately 70% to 80% occur in the occipital region (du Plessis & Volpe, 2018; Huang & Doherty, 2018). The sac protrudes from the back of the head or the base of the neck. The next most common area is the frontal region, with involvement of the orbit, nose, and/or nasopharynx. Encephaloceles can also occur, although uncommonly, in the temporal or parietal areas (Gressens & Hüppi, 2015). Hydrocephalus, which may be present at birth or develop after surgical repair, occurs with 50% of occipital encephaloceles because of alterations in the posterior fossa (Gressens & Hüppi, 2015). Encephalocele may occur in association with chromosomal abnormalities, such as trisomy 13, 18, and 21, Meckel–Gruber syndrome, or Walker–Warburg syndrome (du Plessis & Volpe, 2018).

The protruding sac varies considerably in size; however, the size of the external sac does not necessarily correlate with the presence of neural elements. For example, a large occipital sac may contain minimal neural tissue, whereas a small sac may contain parts of the cerebellum or accessory lobes; some occipital lesions have no neural elements in the sac. Neural tissue generally displays normal gyration and white matter and is connected to the brain by a slender necklike structure (du Plessis & Volpe, 2018; Gressens & Hüppi, 2015). If the sac is leaking CSF at birth, immediate repair is necessary. If the defect is covered by skin, surgery may be delayed until a complete workup, including skull radiography, CT or cranial ultrasonography, MRI, and electroencephalography (EEG), can be performed. Surgical closure helps prevent infection and facilitates feeding and other care. A ventriculoperitoneal shunt is inserted if hydrocephalus is present. Other management includes prevention of infection and trauma and positioning to avoid pressure on the defect. Maintenance of normal body temperature is essential, especially in infants with CSF leakage, because these infants are at risk for thermoregulatory problems caused by evaporative losses. Postoperative management includes assessment of ventilation and perfusion, comfort measures, monitoring of neurologic and motor function, promotion of normothermia, prevention of infection, positioning to prevent pressure on the operative site, and monitoring of the site for CSF leakage. The mortality rate and later outcome are significantly better for infants with anterior defects than for those with posterior defects. The prognosis is poor if significant brain tissue is contained within the sac (Huang & Doherty, 2018).

Families of infants with an encephalocele need initial and continuing support and counseling. Initial parental care involves assisting parents with the shock of the defect and its appearance and with their grief over having an infant with an anomaly, as well as helping the parents deal with the outcome implications of this defect. Nursing care also involves enhancing parent–infant interaction and involving the parents in the infant's care when they are ready. Teaching before discharge includes skin care, positioning, exercises, handling and feeding techniques, and activities to promote growth and development.

Spina Bifida. Spina bifida is a general term used to describe defects in closure of the caudal neural tube that are associated with malformations of the spinal cord and vertebrae. Spina bifida arises from defects in closure of the caudal neuropore during primary neurulation (open defects) or during secondary neurulation (closed defects). Defects range from minor malformations of minimal clinical significance to major disorders that result in paraplegia or quadriplegia and loss of bladder and bowel control. The two major forms of spina bifida are spina bifida occulta and spina bifida cystica.

Spina bifida occulta is a vertebral defect at L5 or S1 that arises from failure of the vertebral arch to grow and fuse between 5 weeks' gestation and the early fetal period. Frequently, only one vertebra is involved in the defect and the spinal cord and nerves are not involved, so there usually are no neurologic symptoms. The dermal layer is intact over the vertebral defect; occasionally, the defect is indicated by a dimple or tuft of hair. Incidence is difficult to determine as many are unrecognized due to minimal/no physical problems arising from the presence of this defect. Spina bifida occulta is often discovered in radiographs of the lumbar and sacral regions. A few individuals have underlying abnormalities of the spinal cord or the nerve roots, or both, such as diastematomyelia or dermal sinus (dermoids; Moore et al., 2015). Diastematomyelia results from the division of the spinal cord or nerve roots in an anteroposterior direction by a bony spicule or cartilaginous band. A dermal sinus is a tract of squamous epithelium that connects to the dura mater and is found in the midline, usually in the lumbosacral area corresponding to the location of the caudal neuropore. A dermal sinus occasionally is recognized at birth, but more often it is diagnosed later, after repeated episodes of meningitis (Danzer et al., 2017; du Plessis & Volpe, 2018).

Spina bifida cystica is a generic term for NTDs characterized by a cystic sac containing meninges or spinal cord elements, or both, along with vertebral defects. Epithelium or a thin membrane covers the sac. As with anencephaly, the incidence has declined in recent years (ACOG, 2017; Moore et al., 2015). Spina bifida cystica can occur anywhere along the spinal column but is seen most often in the lumbar or lumbosacral area. The three main forms of spina bifida cystica are meningocele, MMC, and myeloschisis.

A meningocele involves a sac that contains meninges and CSF, but the spinal cord and nerve roots are in their normal position. Neurologic deficits are not typically associated with meningocele. Meningoceles account for about 5% of spina bifida cystica (Moore et al., 2015).

MMC refers to a sac containing spinal cord or nerve roots, or both, in addition to meninges and CSF and accounts for 80% of spina bifida cystica. The incidence of MMC is 0.3 to 0.72 per 1,000 births (Cavalheiro et al., 2017). This defect occurs around 26 days' gestation, around the time of closure of the caudal neuropore (du Plessis & Volpe, 2018). During development, the nerve tissues become incorporated into the wall of the sac, impairing differentiation of nerve fibers. The spinal cord and/or nerve roots are displaced dorsally, and defects of the muscle and bony structures are present. These lesions are covered with skin or meninges, or both, and are usually located in the lumbosacral area. The level of the impairment of the spinal cord dictates the severity of the neurologic deficit as the nerve tissues below the sac are impaired. The sensory level generally tends to approximate the motor level but may be several segments lower because of differences in the pattern of innervation between sensory and motor fibers (Blackburn, 2018). Approximately 80% of these malformations occur in the lumbar area, which is the final area of neural tube fusion (du Plessis & Volpe, 2018). If the sac is covered with meninges, there is a risk of rupture during delivery, along with leakage of CSF and the risk of infection and dehydration. Individuals with MMC may have motor and sensory impairments of the lower extremities, bowel and bladder dysfunction, hydrocephalus, and spinal/leg alterations such as scoliosis and hip, ankle and foot issues (Cavalheiro et al., 2017). Infants with MMC have altered tone and activity of the lower extremities and may assume a froglike posture. With bowel and bladder involvement, dribbling of urine and feces may be noted. Many infants also have associated Chiari type II malformations with a noncommunicating form of hydrocephalus (Gressens & Hüppi, 2015; Moore et al., 2015). Hydrocephalus

is seen in up to 82% of infants repaired after birth (Cavalheiro et al., 2017).

Chiari type II malformations are defects in neural tube closure involving several anomalies, including displacement of the medulla, fourth ventricle, and lower cerebellum into the cervical canal; bony defects of the occiput, foramen magnum, and cervical vertebrae; and obstruction of the foramen magnum, leading to hydrocephalus (du Plessis & Volpe, 2018; Gressens & Hüppi, 2015). The resulting hydrocephalus is caused primarily by one, or both, of two defects—either a hindbrain malformation blocking normal flow of the spinal fluid from fourth ventricular outflow and/or through the posterior fossa, or there may be aqueductal stenosis causing disruption of normal spinal fluid flow. Chiari type II malformation occurs with most MMCs located at the thoracolumbar, lumbar, and lumbosacral levels.

Management

Immediate management for all NTDs includes stabilization and prevention of trauma to or infection of the sac, if present, and its contents. The infant is monitored for signs of infection, including signs of sepsis or meningitis and localized infection, including redness or discharge from the sac. Warmth and hydration are provided, and fluid and electrolyte status are monitored. **Emergency Alert: These infants are at greater risk of hypothermia and dehydration because of the open lesion, which lacks the normal protective skin covering.** Infants with NTDs may have evidence of hydrocephalus at birth. Ultrasonography, CT, or MRI can be used to determine the size of the ventricular system, to rule out Chiari type II malformation, and to monitor ventricular status and the development of hydrocephalus. Renal dysfunction may develop as a result of recurring urinary tract infections. Infants with NTDs may also have cardiac, intestinal, orthopedic, and other neurologic anomalies (Blackburn, 2018; du Plessis & Volpe, 2018; Gressens & Hüppi, 2015; Hockley & Salanki, 2009).

The infant with NTD is positioned prone or on the side to reduce tension on the sac. A roll between the legs at hip level assists in maintaining abduction of the legs; a foot roll is used to maintain the feet in a neutral position. Change of position from prone to side lying or side to side, as well as range-of-motion exercises, helps prevent skin breakdown and contractures. If the infant must be temporarily placed in a supine position for a procedure, a donut roll can be used to prevent pressure on the sac. Postoperative positioning also involves use of the prone or sidelying position, maintenance of body alignment, prevention of hip abduction, and prevention of pressure on the operative site with holding. Lumbar/sacral defects must be kept free of fecal or urine contamination. Meticulous skin care, with attention to keeping the skin clean and dry and removing urine and stool, helps prevent skin breakdown and infection. The timing and characteristics of urination and stool excretion are observed to help determine the degree of deficit.

For most infants with MMC, immediate closure and aggressive care constitute appropriate management (Cavalheiro et al., 2017; Hockley & Salanki, 2009; Huang & Doherty, 2018; Piatt, 2010). Less infection and better outcomes are reported with MMC repair within 48 hours of birth (Cavalheiro et al., 2017). Unless the defect is severe or is associated with multiple life-threatening anomalies, more than 90% of infants with MMC survive the neonatal period. Immediate closure reduces the risk of infection and improves the prognosis by reducing further deterioration of the spinal cord and nerve tracts. Early closure also facilitates caregiving. A large defect may require several surgical procedures for complete closure. If the defect is completely covered by epithelium, surgery may be delayed for a short period so that function can be evaluated further. All infants with NTDs are evaluated and monitored for hydrocephalus. Urologic function and renal function also are assessed continually. All infants with involvement of the spinal cord or nerve roots, or both, require multidisciplinary follow-up and continuing care to deal with neurologic, urologic, orthopedic, and psychologic problems (Hockley & Salanki, 2009; Huang & Doherty, 2018; Piatt, 2010).

Families of infants with NTDs need initial and continuing support and counseling. Initial parental care involves assisting parents with the shock of having an infant with a defect and its appearance and with their grief over having an infant with an anomaly. Nursing care also involves enhancing parent–infant interaction and involving the parents in the infant's care when they are ready. Teaching before discharge includes skin care, positioning, exercises, handling and feeding techniques, and provision of activities to promote development. Many areas have spina bifida associations and parent-to-parent support programs to which parents can be referred for peer support.

In utero repair of MMC is performed before 26 weeks in some centers to reduce postnatal complications such as hindbrain herniation, hydrocephalus, and urologic dysfunction. In utero intervention is based on the hypothesis that long-term outcomes are related to both the primary defect (MMC) and secondary complications such as damage to exposed neural tissue along with development of Chiari II and hydrocephalus, and that in utero surgery may reduce this secondary damage (du Plessis & Volpe, 2018). Significant improvement in sensorimotor function has not been reported and an increase in obstetrical complications, such as preterm labor, oligohydramnios, premature rupture of the membranes, and surgical risks involved, were reported in several small studies (Adzick et al., 2011; Bebbington, Danzer, Johnson, & Adzick, 2011; Czeizel et al., 2011; Danzer, Johnson, & Adzick, 2012; Hockley & Salanki, 2009). In an effort to determine whether prenatal repair of MMC improved outcomes over postnatal surgical repair, a large, prospective randomized clinical trial, the Management of Myelomeningocele Study, was done at three maternal–fetal surgery centers (Adzick et al., 2011; Danzer et al., 2012). The results of this study showed that in utero repair of MMC reduced the need for postnatal shunting and improved motor outcomes at 30 months but was associated with maternal and fetal risks. Maternal risks included oligohydramnios, chorioamniotic separation, placental abruption, and spontaneous membrane rupture. Fetal complications included premature delivery, with an average gestational age of 34.1 versus 37.1 weeks in postnatal surgical group, and nearly 13% delivered before 30 weeks' gestation (vs. none in postnatal surgical group), and respiratory distress syndrome, which was likely primarily attributable to prematurity. No other significant fetal/neonatal complications were reported for the in utero surgical group.

In utero surgery was associated with a decreased need for ventriculoperitoneal shunt, less risk of moderate-to-severe brain herniation, improved motor function and ambulatory status, and improved mental development (Adzick et al., 2011; Cavalheiro et al., 2017; Danzer et al., 2012). The prenatal surgical group required more procedures for delayed spinal cord tethering than did the postnatal surgical group. Parent-reported self-care and mobility were also significantly better in the prenatal surgical group than in the postnatal group. There were no differences in later cognitive scores between groups (Adzick et al., 2011; Danzer et al., 2012). Long-term follow-up of infants with fetal surgery at 10 years of age found that 79% were community ambulators, 14% wheelchair dependent, and 26% had normal bladder function (Danzer et al., 2016). Since fetal surgery requires a specialized, multidisciplinary team, it is only available in a limited number of centers, and, as previously noted, is associated with increased maternal and fetal complications (Cavalheiro et al., 2017). Work is ongoing on

improving surgery techniques such as examination of less invasive endoscopic techniques and use of a biocellulose patch to reduce maternal and perinatal complications (Cavalheiro et al., 2017; du Plessis & Volpe, 2018).

The prognosis associated with NTDs varies with the level and severity of the defect. However, these limitations are changing as a result of improved perinatal management and new technologies, and more children are ambulatory now than they were previously. The prognosis has also improved with the current early and aggressive treatment of infants, especially in those without major cerebral lesions, hemorrhage, infection, high spinal cord lesions, or advanced hydrocephalus (du Plessis & Volpe, 2018; Huang & Doherty, 2018).

Prosencephalic Development

Prosencephalic development, or ventral induction, involves early development of the brain and ventricular system, which occurs during the second to third month of gestation (peaking at 5–6 weeks). The brain develops from the cranial end of the neural tube, beginning at the end of the fourth week. During this period, the three primary brain bulges (or vesicles) and cavities are formed, after fusion of the neural folds in the cranial area.

The primary brain bulges are the forebrain (prosencephalon), the midbrain (mesencephalon), and the hindbrain (rhombencephalon). During the fifth week, the forebrain divides into two secondary vesicles, the telencephalon and the diencephalon, and the hindbrain divides into the metencephalon and the myelencephalon. The derivatives of each of these structures form the structures of the definitive brain. The third and fourth ventricles are formed from cavities within the rhombencephalon and diencephalon; the aqueduct of Sylvius links these two ventricles. The lateral ventricles arise from cavities in the cerebral hemispheres and are connected to the third ventricle by the foramen of Monro (see Figure 15.1). Early growth of the neural tube is most rapid in the forebrain region. To give these structures space to grow, the neural tube bends at several points, forming the mesencephalic (midbrain area), cervical (junction of the hindbrain and spinal cord), and pontine flexures (Huang & Doherty, 2018; Moore et al., 2015). The cerebellum arises from the rhombencephalon.

Disorders of Prosencephalic Development. Malformations that occur during this period generally are thought to arise around the fifth to sixth weeks of gestation. Infants with these anomalies have a poor prognosis, and many are lost in early pregnancy or are stillborn. Malformations of the forebrain include holoprosencephaly and holotelencephaly. Holoprosencephaly is an abnormality in cleavage of the hemispheres that arises from genetic or possibly environmental alterations. Failure of horizontal, transverse, and sagittal cleavage of the prosencephalon disrupts formation of the telencephalon and the diencephalon and their derivatives. The resultant brain has a single monoventricular cerebral mass enclosed by a membrane; aplasia of the optic tract with absence of the olfactory tracts and bulbs, and agenesis of the corpus callosum, also is characteristic. Microcephaly, hydrocephaly, and facial anomalies also may be seen (Huang & Doherty, 2018; Moore et al., 2015). With holotelencephaly, the parts of the brain that develop from the telencephalon form a single spheroid structure; the diencephalon and its derivatives are less affected. Congenital hydrocephalus and agenesis of the corpus callosum can also arise during this period. Development of the face is associated with prosencephalic development of the CNS; consequently, alterations in brain development often result in facial malformations (Huang & Doherty, 2018; Kanekar, Shively, & Kaneda, 2011).

Neuronal Proliferation

The development of neurons and glial cells involves proliferation in the germinal matrix; migration (to their final destination) in the next stage of CNS development; differentiation of glial cells (during the period of organization) into specific cell types; alignment of neurons; and the development of interneuron and glial–neuron relationships. Cerebellar neurons arise within the cerebellar germinal matrix. The peak period of neuronal proliferation in the cerebral area lasts from 2 to 4 months' gestation, followed by glial proliferation beginning at 15 weeks' gestation, and in the cerebellum from 2 months' gestation to 10 months postnatal age (Yuskaitis & Pomeroy, 2017). During this stage, further development occurs in the cerebral subventricular and ventricular zones, where neurons and glial cells are derived from stem cells in the cerebral germinal matrix. Initial proliferation involves primarily neurons and radial glia, which are needed for neuron migration. Proliferation of other glia and their derivatives (astrocytes and oligodendrocytes) occurs intensively during the stage of organization, at 5 to 8 months' gestation. During the most intense period of proliferation, before 32 to 34 weeks' gestation, the periventricular area receives a large proportion of the cerebral blood flow. This area is vulnerable to hemorrhage (see section on Germinal Matrix-Intraventricular Hemorrhage) in preterm infants (Blackburn, 2018; Fleiss, Stolp, Mezger, & Gressens, 2018; Poduri & Volpe, 2018a).

Disorders of Neuronal Proliferation. Disorders of proliferation arise from inadequate or excessive proliferation of neuronal derivatives, glial derivatives, or glial cell derivatives. Insults may alter the neuronal-glial stem cells, which reduces the number of neurons or glial cells, or may alter cell growth, which results in smaller cells. The resulting disorders include micrencephaly, macrencephaly, and neurofibromatosis (Huang & Doherty, 2018; Poduri & Volpe, 2018a). Micrencephaly may be due to a reduction in either the size or number of stem cells (Huang & Doherty, 2018; Poduri & Volpe, 2018a). Micrencephaly vera is associated with a small brain caused by a decrease in the size of the proliferating units as a result of genetic or environmental factors and occurs at 2 to 4 months' gestation. These infants often do not have marked neurologic deficits or seizures during the neonatal period, and in general the brain is well formed; however, the infants later manifest mental delays. Genetic factors associated with micrencephaly vera include autosomal recessive or dominant trait, X-linked recessive trait, or translocation. Micrencephaly vera is associated with environmental factors such as irradiation, metabolic alteration, maternal rubella, fetal alcohol syndrome, maternal cocaine use, and maternal phenylketonuria with elevated phenylalanine levels during pregnancy.

Macrencephaly results in a large brain size because of excessive proliferation of neuronal elements or nonneuronal elements, or a combination of both. Macrencephaly is associated with genetic disorders including Beckwith–Wiedemann syndrome, Sturge–Weber syndrome, Weaver syndrome, and achondroplasia; chromosomal disorders such as Klinefelter and fragile X syndromes, and partial trisomy of chromosome 7; and neurocutaneous disorders, such as neurofibromatosis. Neurofibromatosis is an autosomal dominant genetic disorder involving excessive proliferation of nonneuronal elements in the CNS and mesodermal structures of the body, with cutaneous stigmata (Blackburn, 2018; Huang & Doherty, 2018; Kanekar, Kaneda, & Shively, 2011; Poduri & Volpe, 2018a). Neurofibromatosis often presents with alterations to skin pigmentation (café-au-lait macules), Lisch nodules of the iris, buphthalmos (enlarged eyeball), skin nodules, and multiple benign neurofibromas. Infants with more than five café-au-lait macules larger than 5 mm in diameter at birth should be further evaluated for neurofibromatosis. Neurofibromatosis is associated

with learning disabilities and, later in life, possible development of skeletal abnormalities, vascular disease, CNS tumors, or malignant peripheral nerve sheath tumors (Blackburn, 2018; Jett & Friedman, 2010; Poduri & Volpe, 2018a).

Neuronal Migration

The peak period for the neuronal migration stage is 3 to 5 months' gestation in the cerebrum and 4 months' gestation to 10 months postnatally in the cerebellum (Yuskaitis & Pomeroy, 2017). This stage is characterized by the movement of millions of cells from their point of origin in the subependymal germinal matrix of the periventricular region to their eventual loci in the cerebral cortex (see Figure 15.1) and similar movements of neurons within the cerebellum from their point of origin to their final location. The process of neuronal migration is critical to the formation of the neocortex, gyri, and deep nuclear structures. Development of the gyri and sulci follows a predictable pattern that is linked to gestational age. At 21 to 25 weeks' gestation, the central ventricles are large and the brain agyric; gyral development begins by the end of this period (Blackburn, 2018; Poduri & Volpe, 2018b).

The mechanisms that guide neuronal migration are not completely understood, but they are mediated by signaling proteins, surface molecules, and receptors on both the neurons and the radial glia (Poduri & Volpe, 2018b; Valiente & Marin, 2010). The migration of the neurons to both the cortex and within the cerebellum is assisted by the radial glia (Poduri & Volpe, 2018b). Radial glia act as guides for migrating cells and then later transform into astrocytes (Poduri & Volpe, 2018b; Valiente & Marin, 2010). The cerebral cortex has essentially achieved its full complement of neurons by 24 weeks' gestation; however, GABAergic neuron migration continues to near term (Fleiss et al., 2018; Poduri & Volpe, 2018b). Later migration predominantly involves glial cells.

Disorders of Neuronal Migration. Errors or exogenous insults before or after birth can alter migration of neurons and glial cells. Alterations in migration can result in hypoplasia or agenesis of the corpus callosum, agenesis of a part of the cerebral wall (schizencephaly), or gyral anomalies (pachygyria, lissencephaly, and polymicrogyria). The preterm infant may be especially vulnerable to gyral alterations. Rapid development of the gyri begins at 26 to 28 weeks' gestation and continues through the third trimester into the postbirth period. Development of gyri results in a marked increase in cerebral surface area (Fleiss et al., 2018; Poduri & Volpe, 2018b; Valiente & Marin, 2010).

Organization

The peak period for organization is about the fifth month of gestation to a few years after birth. However, organizational processes continue throughout childhood, particularly in the cerebellum. Some processes, such as synaptogenesis, continue until death. Organizational processes allow the nervous system to act as an integrated whole. These processes include (a) establishment of subplate neurons; (b) attainment of the proper alignment, orientation, and layering of cortical neurons; (c) arborization or differentiation and branching of axons and dendrites; (d) differentiation of glial cells; (e) development of synaptic connections ("wiring" of the brain) with balancing of excitatory and inhibitory synapses; (f) gyral development; and (g) cell death and selective elimination of neuronal processes (Blackburn, 2018; Fleiss et al., 2018; Kinney & Volpe, 2018c).

Subplate neurons are critical structures in the development of the neocortex, with maximal size and vulnerability reached by 24 to 32 weeks (Fleiss et al., 2018; Kinney & Volpe, 2018c). Thus, subplate neurons are vulnerable to perinatal injury. Subplate neurons serve as transient "way stations" by providing a place of synaptic contact for axons that ascend from the thalamus and other areas in which connecting cortical neurons are not yet in place, are a site of initial synaptogenesis between areas within the cortex, produce axons for the corpus callosum, and are critical in guiding axons to their final loci and in establishing functional connections between different areas of the brain (Fleiss et al., 2018; Kinney & Volpe, 2018c; Volpe, Kinney, Jensen, & Rosenberg, 2011). Subplate neurons may be damaged in preterm infants with periventricular leukomalacia (PVL; Fleiss et al., 2018).

Glial cells serve as supportive structures with the CNS. The three forms of glia are (a) myelin-producing glia (oligodendrocytes in the CNS; Schwann cells in the peripheral nervous system); (b) guiding glia (radial glia for neuron migration during CNS development; Schwann cells for guiding peripheral nerves); and (c) "clean-up" glia (astroglia and microglia), which remove waste and dead tissue. Astroglia also provide support for neurons, assist in integration of information within the CNS, and are important in the structure and function of the blood–brain barrier. Astrocyte proliferation peaks at 26 to 28 weeks (Fleiss et al., 2018). Microglias are capable of phagocytosis and function as brain macrophages and may be involved in developmental apoptosis (Blackburn, 2018; Kinney & Volpe, 2018c; Volpe et al., 2011). When activated by inflammation or ischemia, as occurs with white matter injury (WMI), microglia can lead to further cellular injury. During the premyelinating period, oligodendrocytes are especially vulnerable to hypoxic-ischemic injury (see section on White Matter Injury in Preterm Infants; Back & Volpe, 2018; Fleiss et al., 2018; Volpe et al., 2011).

The process of cell death and selective elimination of neuronal processes is important in adjusting the size of individual neurons to their anticipated need. It is also an important component of brain plasticity in infants. In the developing brain, neuronal processes targeted for elimination can be saved if they are needed because of damage to other processes; by this means, functional ability is preserved. Excitatory neurotransmitters, such as glutamate, mediate neural development and organization by acting on *N*-methyl-D-aspartate (NMDA) receptors, and also likely, on GluR2-deficient alpha-amino-3-hydroxyl-5-methyl-4-isoxazolenpropionic acid (AMPA) receptors and by opening voltage-dependent calcium channels (Kinney & Volpe, 2018c).

A striking increase in the cerebral cortical volume and gyral changes occurs during this period of development and with organization of cortical neurons, especially from around 28 to 40 weeks' gestation. During this time there is a fourfold increase in cortical gray matter volume (Kinney & Volpe, 2018c).

Disorders of Organization. Organization of the brain is susceptible to insults from errors of metabolism, abnormal chromosomes, and perinatal insults. Organizational processes are particularly vulnerable in the preterm infant being cared for in an intensive care unit during this period. Alterations in arborization and wiring of the brain can lead to hypersensitivity, poorly modulated behavior, and all-or-nothing responses. Alterations in organization are seen in infants with Down syndrome-Trisomy 21, who have abnormal development of the axons and dendrites and altered synaptic formation, fragile X syndrome, Angelman syndrome (microdeletion on the long arm of maternal chromosome 15), Duchenne muscular dystrophy, intellectual disabilities (with or without seizures), and Rett syndrome.

Myelination

The myelination stage involves development of myelin sheaths around nerve fibers in the nervous system. Oligodendrocytes myelinate the nerve fibers of the CNS and Schwann cells myelinate

the nerve fibers of the peripheral nerves. The lipoprotein plasma membranes of these cells wrap themselves around the nerve fibers for several layers. Myelination of fiber tracts tends to occur before maturation of functional ability (Moore et al., 2015; Kinney & Volpe, 2018b).

Myelination begins early in pregnancy and continues into adulthood. Myelination predominates between 8 months' gestation and 2 years of age, with the peak period thought to be occurring within the first 8 postnatal months of life. However, myelination continues into adolescence and early adulthood (Kinney & Volpe, 2018b). This process begins before birth in the peripheral areas, first in the peripheral motor nerves and then in the peripheral sensory nerves. Myelination also begins before birth in the CNS, moving upward from the brainstem and cerebellum. In the CNS, myelination occurs first in the sensory areas and then in the motor areas. Myelination of ascending pathways in the spinal cord, brainstem, and thalamus is completed by about 30 weeks' gestation, and myelination from the thalamus to the cortex is completed by 37 weeks (Kinney & Volpe, 2018b). From birth to adulthood, myelination proceeds within the cerebral hemispheres in conjunction with the development of higher associative and sensory functions. Myelination is important in most nerve tracts in the CNS because it insulates individual fibers to enhance specificity of connections, increases the number of alternative pathways, and markedly increases the speed of transmission (Blackburn, 2018; Kinney & Volpe, 2018b). This has implications for neonatal pain management, particularly for preterm infants.

Disorders of Myelination. Myelination is susceptible to damage from diverse exogenous influences, particularly malnutrition, which can lead to a range of neurologic deficits in which hypoplasia of the cerebral white matter occurs. Primary hypoplasia of the white matter with vacuolization of the myelin occurs in inadequate postnatal nutrition, congenital hypothyroidism, 18q-syndrome, and amino and organic acidopathies such as maple syrup urine disease, homocystinuria, and phenylketonuria. This defect in myelination can lead to severe neurologic deficits in these infants (Kinney & Volpe, 2018b).

Neurologic Assessment

Assessment of neurologic function is an initial step in evaluating an infant's response to the transition to extrauterine life and the impact of perinatal events and pathophysiologic problems on the central and peripheral nervous systems. Assessment of neurologic function and identification of dysfunction encompass several components, including the history, physical examination, neurologic examination, laboratory tests, and other diagnostic techniques.

History

Risk factors noted in the maternal, obstetrical, and neonatal histories can be useful in identifying infants at risk for neurologic dysfunction and specific pathophysiologic factors. Specific risk factors for each problem discussed here are identified later in individual sections. General maternal or family historical factors that must be examined include a family history of NTDs; chromosomal or genetic abnormalities or other malformations; maternal substance abuse; chronic maternal health problems; maternal age, nutritional status, and exposure to teratogens; and the outcome of previous pregnancies (Heaberlin, 2019).

Obstetrical risk factors include prematurity, postmaturity, placental problems (e.g., abruptio placentae and placenta previa), use of analgesia or anesthesia, and maternal problems (e.g., infection, hypertension, and substance abuse). A large for gestational age (LGA) infant, prolonged or precipitate labor, forceps delivery, and abnormal presentation increase the risk of birth trauma and hemorrhage. Alterations in intrauterine growth and polyhydramnios may be present with an infant who has a CNS malformation. Fetal distress, hypoxia, ischemia, and low Apgar scores are associated with intracranial hemorrhage and HIE (Back & Miller, 2018; Blackburn, 2018; Inder & Volpe, 2018a, b).

Because neurologic dysfunction also can arise from postnatal problems, the infant's postnatal history is evaluated for status at birth, whether resuscitation was required, ischemic or hypoxic episodes, shock, hypoperfusion with or without, hemorrhage, infection, and metabolic or electrolyte aberrations. The infant's record is also reviewed for clinical signs, such as seizures or alterations in activity, tone, and state, which are associated with neurologic dysfunction (Heaberlin, 2019; Walker, 2018).

Physical Examination

A comprehensive physical examination is an important component of the assessment of any infant at risk for, or showing evidence of, neurologic dysfunction. Infants are examined especially for evidence of infection and birth trauma, such as ecchymosis, edema, lacerations, and fractures. Temperature, blood pressure, color, and respiratory patterns are also assessed. The infant is examined for signs of vascular alterations, such as a port-wine stain along trigeminal nerve branches, which may indicate Sturge–Weber syndrome. The characteristics of the infant's cry (e.g., robustness, presence in response to aversive stimuli, and pitch) may also be useful. Funduscopic examination may be performed to assess for chorioretinitis (associated with intrauterine viral infection), papilledema (seen with cerebral edema, although less reliably in neonates), and congenital anomalies (Amiel-Tison & Gosselin, 2009; Walker, 2018).

Specific parameters that are particularly important for the nurse to assess in infants with neurologic problems are (a) the head size, shape, and rate of growth; (b) the sutures and fontanelles; (c) whether major and minor anomalies are present; and (d) the vertebral column. Because CNS anomalies often are associated with other anomalies and syndromes, the infant is also examined for major anomalies of body systems and for isolated or clustered minor malformations, such as low-set or abnormally shaped ears, micrognathia, and hypertelorism of the eyes. The vertebral column is inspected and palpated for evidence of NTDs. Signs that may indicate an underlying defect include hair tufts, dimples, and fistulae (Amiel-Tison & Gosselin, 2009; Walker, 2018).

Head Size, Shape, and Rate of Growth. The monitoring and plotting of head circumference are basic components of healthcare for all infants, regardless of gestation or health status. The largest circumference is measured, which usually is the occipitofrontal circumference, about 1 cm above the eyes. The measurement is plotted on the appropriate growth grid for the infant's gender and gestation. The most accurate measurements are made with a metal or plastic tape marked in centimeters. Paper tapes tend to stretch and are less accurate but can be used for initial screening and for infants whose head size raises no concern. The occipitofrontal circumference generally ranges from 32.6 to 37.2 cm in term infants. Infants with caput succedaneum or overriding sutures may need to be remeasured after 3 days to obtain a more accurate measurement (Amiel-Tison & Gosselin, 2009). The head usually grows 0.1 to 0.6 cm/week in infants 24 to 40 weeks' gestation (Ditzenberger, 2015).

Serial measurements must be made to identify changes in the rate of growth as well as in size. Changes in the growth rate are important because an infant may have a significant increase or decrease in head growth but remain within the 10th to 90th

percentiles on standard head growth grids. The occipitofrontal circumference should be measured several times over the first days after birth to obtain an accurate baseline after molding and edema from birth have resolved. Head circumference is measured weekly on preterm or ill infants. More frequent measurements may be made if the infant is at risk of developing progressive ventricular dilatation. Head shape can also reflect perinatal events and specific anomalies. The forces of labor and delivery may deform the head, but these changes are transient and disappear within a few days. Infants with craniosynostosis (premature closure of one or more sutures) and hydrocephalus have abnormal head configurations (Evans, Hing, & Cunningham, 2018; Johnson, 2019).

Sutures and Fontanelles. The entire head is inspected and palpated, and each suture and fontanelle is assessed. The anterior fontanelle is assessed while the infant is in a quiet state and in a semi-upright or sitting position. The fontanelle should be open, soft, and flat. Pulsation may be felt normally in a newborn but can be associated with elevated blood pressure. **Emergency Alert: A sunken or depressed fontanelle is seen with dehydration, and a bulging fontanelle is noted with increased intracranial pressure (ICP).** The anterior fontanelle usually is diamond shaped and may be small at birth if molding and overriding of the sutures are present; the size increases within a few days to the usual dimensions seen in term infants (i.e., 3–4 cm long by 1–3 cm wide). The anterior fontanelle closes at 8 to 16 months of age. The anterior fontanelle may bulge slightly with increased tension when the infant cries and may be slightly depressed when the infant is placed in an upright position. The posterior fontanelle closes any time from 8 months' gestation to 2 months after birth. If open at birth, it is 1 to 3 cm wide and has a triangular shape. In rare cases, a "third fontanelle" may be palpated along the sagittal suture between the anterior and posterior fontanelles; this is not a true fontanelle but a defect in the parietal bone. It can be palpated in normal infants, but it is also seen in infants with Down syndrome or hypothyroidism (Heaberlin, 2019). A 4- to 5-mm separation (up to 1 cm) of all the sutures except the squamosal (temporoparietal) suture is normal in the newborn. The squamosal suture should not be separated more than 2 to 3 mm, especially in the term or near-term (late preterm) infant. Overriding of the bones and molding from delivery may modify this finding in the first few days after birth. Abnormal findings include persistence of suture separation over time, increased separation of the sutures, and separation of the squamosal suture by more than 2 to 3 mm. With increased ICP, separation of the sutures occurs in a specific order: sagittal, coronal, metopic, lambdoidal, and squamosal; therefore, separation of the squamosal suture is the most clinically significant (Amiel-Tison & Gosselin, 2009). The cranial bones are inspected and palpated so that fractures, extradural hemorrhage, edema, and areas of uneven ossification of the cranial bones or craniotabes can be identified.

Neurologic Examination

The neurologic examination is useful for evaluating for the presence and determining the extent of neurologic dysfunction in the neonate, for monitoring recovery, and as a prognostic indicator. Factors such as gestational age, health status, the infant's state, medications, and timing of feedings must be considered in the interpretation of neurologic findings. Parameters examined in the assessment of neurologic status include level of consciousness, activity, tone, posture, reflexes, and evaluation of selected cranial nerves (Amiel-Tison & Gosselin, 2009; Heaberlin, 2019; Walker, 2018). The optimum state of the infant during a neurologic examination is quiet and alert, after awakening naturally from a sleep state. It may be difficult to find such a perfect moment, and often the infant must be aroused from a sleep state or quieted from a state of heightened arousal. It is important to determine the state of the infant prior to a neurologic examination, since the infant's level of alertness has an effect on the interpretation of the infant's neurologic status (Amiel-Tison & Gosselin, 2009; Heaberlin, 2019; Walker, 2018).

Observation of State: Level of Consciousness. Neurologic insults frequently alter the infant's level of consciousness. The level of consciousness may range from normal states of consciousness for gestation to hyperexcitability, irritability, lethargy, hyperalertness, and stupor or coma. The three clinical levels of consciousness that best correlate with outcome are hyperalertness, lethargy, and stupor or coma. In the hyperalert state, the infant has an increased sensitivity to sensory stimulation, with wide-open eyes but with a diminished blink response and ability to fixate and follow. A lethargic infant responds to tactile and noxious stimuli, but the responses are delayed. A stuporous or obtunded infant's response is limited to noxious stimuli, and a comatose infant shows no response to tactile or noxious stimuli (Amiel-Tison & Gosselin, 2009; Walker, 2018). Hyperexcitability and irritability can be assessed by noting an infant's response to caregiving actions and medical procedures, as well as the baby's state between caregiving intervals to assess the infant's ability to use self-consoling measures.

Posture, Tone, and Activity. Because normal tone requires integrated functioning of the entire nervous system, disturbances in either the central or peripheral nervous system may manifest in alterations in neonatal position, tone, and activity (Walker, 2018). The infant first is assessed while lying in a resting position. A frog-leg position while supine is seen in immature infants, after breech delivery, and in infants who have experienced severe asphyxia or who have major health problems or neuromuscular disorders (Amiel-Tison & Gosselin, 2009; Walker, 2018). The quality and symmetry of activity with spontaneous and elicited movement are assessed. Alterations in symmetry of the trunk, face, and extremities at rest or with spontaneous movement suggest congenital anomalies, birth injury, or neurologic insult. Tight fisting is an abnormal sign. A cortical thumb (inside thumb on closure of the hand) may be normal, but it is abnormal if persistent. Opisthotonos and decerebrate or decorticate posturing may also occur (Amiel-Tison & Gosselin, 2009; Heaberlin, 2019; Johnson, 2019; McAdams & Traudt, 2018).

Abnormal movements include seizure activity, jitteriness, and tremors, although the last two findings often are normal. Tremors and jitteriness must be differentiated from seizures. The characteristic movements seen with tremors in the neonate vary with the underlying disorder. Tremors associated with metabolic abnormalities usually are low-amplitude, high-frequency movements, whereas tremors associated with CNS complications usually are high-amplitude, low-frequency movements. Jitteriness is a common finding in infants because of the lack of myelination of the pyramidal tracts. A major function of these tracts is to inhibit spinal reflexes. In the neonate, these unmyelinated respond to central arousal with generalized peripheral hyperexcitability. Jitteriness is stimulus sensitive and is not marked by gaze or eye deviations. The predominant movement in jitteriness is tremulousness, rather than the clonic movement seen in seizures, which ceases with passive flexion. Spontaneous or elicited movement can set off tremors. Tremors can also be associated with metabolic abnormalities, asphyxia, or drug withdrawal (Heaberlin, 2019; Natarajan & Gospe, 2018).

Resting, passive, and active tone are assessed. Resting tone is evaluated by observing the infant at rest in a supine position. Passive tone is evaluated by examining extensibility, which involves maneuvers used in the neuromuscular component of the

assessment of gestational age. Assessment of active tone involves altering the infant's posture to obtain directed motor responses (Amiel-Tison & Gosselin, 2009; Volpe, 2018a).

Common maneuvers are righting reactions of the legs and trunk and examination of neck flexors and extensors. Righting reactions are elicited by holding the infant upright with the feet on a firm surface. The infant's ability to straighten the legs and trunk is assessed. Neck flexors and extensors are assessed using the pull-to-sit maneuver (Amiel-Tison & Gosselin, 2009; Heaberlin, 2019; Volpe, 2018a; Walker, 2018). Infants with peripheral nerve injuries, neuromuscular disorders, alterations at the neuromuscular junction, and spinal cord injuries tend to be hypotonic and have muscle weakness. Infants with CNS disturbances secondary to asphyxia, intracranial hemorrhage, chromosomal disorders or other genetic defects, or metabolic disturbances tend to be hypotonic without muscle weakness (Amiel-Tison & Gosselin, 2009; Dastgir, Chan, & Darras, 2012; Volpe, 2018a; Walker, 2018). Hypertonia is seen less often than hypotonia in neonates with neurologic problems. Marked extensor hypertonia with arching of the back (opisthotonos) may be seen in association with severe hypoxic-ischemic injury, bacterial meningitis, or massive intraventricular hemorrhage (IVH; Amiel-Tison & Gosselin, 2009; Heaberlin, 2019; Johnson, 2019; Volpe, 2018a; Walker, 2018).

Reflexes. In infants with neurologic dysfunction, primary and tendon reflexes may be diminished, absent, or accentuated. Primary reflexes are affected by gestational age, but all are present to some degree by 28 to 32 weeks' gestation and include sucking, grasping, crossed extension, automatic walking (stepping), and the Moro reflex. These reflexes should be present, symmetric, and reproducible in the neonatal period and should gradually disappear during infancy (Amiel-Tison & Gosselin, 2009). The tendon reflexes assessed in the neonate are the biceps, knee, and ankle jerk. All should be present after about 33 weeks' gestation, but are not very helpful beyond confirming symmetry in the neonatal period (Amiel-Tison & Gosselin, 2009; Hoppe & Benedetti, 2018; Volpe, 2018a; Walker, 2018).

Examination of Selected Cranial Nerves. Full cranial nerve assessment generally is not performed on the neonate. However, the function of these nerves can be evaluated using several relatively simple maneuvers: fixation and following, pupillary responses, doll's eye response, hearing, vestibular response, and suck and swallow (Table 15.2; Amiel-Tison & Gosselin, 2009; Evans et al., 2018; Heaberlin, 2019; Johnson, 2019; Volpe, 2018a; Walker, 2018).

Clinical Signs Associated With Neurologic Dysfunction. Clinical manifestations of neurologic dysfunction can be specific or nonspecific. Five types of clinical signs are commonly seen in infants with neurologic problems: (a) CNS depression, (b) hyperirritability, (c) increased ICP, (d) seizures, and (e) movement alterations. Seizures are discussed later. Signs and symptoms of CNS depression, hyperirritability, increased ICP, and movement alterations are listed in Table 15.3.

Diagnostic Techniques

Diagnostic techniques that may be used with infants suspected of neurologic problems include neurophysiologic studies, structural brain imaging and assessment of cerebral blood flow, and laboratory tests. Neurophysiologic studies used in the neurologic assessment of the newborn include brainstem auditory evoked responses, visual evoked responses, somatosensory evoked responses, and EEG and amplitude-integrated EEG (aEEG; Neil & Inder, 2018; Trollmann, Nüsken, & Wenzel, 2010). The brainstem auditory evoked response test is the reflection of the electrical events generated in the auditory pathways detected via small external sensors and indicates the response of the infant to auditory stimulus. This test is easily performed and is currently the most often used technique for routine hearing screening in newborn nurseries. Visual evoked and somatosensory evoked responses are part of a more extensive neurologic examination to aid in determining the extent of the disturbance in the vision and peripheral sensation (Neil & Inder, 2018; Trollmann et al., 2010; Volpe, 2018a). EEG and aEEG will be discussed in the section on neonatal seizures.

The three types of brain structural imaging most often used are ultrasonography, CT, and MRI. Head, or cranial, ultrasound examination is used most often to evaluate intracranial structures and is most frequently the imaging modality of choice to evaluate germinal and IVH in the premature infant, with an estimated 90% accuracy level (Neil & Inder, 2018; Ramenghi & Hüppi, 2009). Ultrasonography is portable, safe, convenient, and readily available at the bedside, utilizing nonionizing radiation with minimal/no need for sedation. Cranial and sagittal images can be evaluated by means of the anterior fontanelle and PVL by means of the posterior fontanelle. Doppler sonography, which is done as part of a complete head ultrasound, can be used to evaluate cerebral blood flow. Head ultrasonography is not generally useful for evaluating the posterior fossa and intraparenchymal and meningeal areas (Koufman, Zanelli, Cantey, & Sanchez, 2012; Neil & Inder, 2018; Neil & Volpe, 2018; Ramenghi & Hüppi, 2009). CT uses ionizing radiation coupled with computerized image reconstruction to provide high-resolution images within a few minutes of scanning. A CT of the newborn brain provides information regarding calcifications and cranial bony abnormalities, most parenchymal disorders, hemorrhage or fluid in the subdural and subarachnoid spaces, and most posterior fossa lesions. The MRI, which uses nonionizing radiation, is useful for diagnosing many abnormalities, some of which may be missed by sonography or CT, such as partial agenesis of the corpus callosum, arteriovenous malformations, acute or chronic focal cerebral ischemic lesions (infarcts), venous thrombosis, PVL, hemorrhagic lesions, and virtually all lesions in the posterior fossa and spinal cord (Girard & Raybaud, 2011; Koufman et al., 2012; Neil & Inder, 2018; Neil & Volpe, 2018). Both CT and MRI require transportation and sedation, however, which may prove to be detrimental to the critically ill infant. Using these modalities often necessitates waiting until the infant has recovered from the initial critical condition to be performed (Neil & Inder, 2018; Neil & Volpe, 2018).

Laboratory tests are performed to assist in the diagnosis of specific neurologic disorders and to identify underlying causes. The CSF is examined for signs of hemorrhage (increased red blood cells, increased protein, decreased glucose, and xanthochromia) and to rule out infection (culture, turbidity of the fluid, and increased or decreased white cells, protein and/or glucose; Gomella, Cunningham, & Eyal, 2009). Xanthochromia often is a late sign and may reflect an elevated protein level rather than the presence of blood. Other laboratory evaluations include complete blood count with differential (e.g., white and red blood cell counts, hemoglobin, hematocrit [Hct], neutrophils, bands, and platelet count), serum glucose and calcium levels, electrolyte levels, blood gases, and acid–base status. A sepsis workup or screening for toxoplasmosis, rubella, cytomegalovirus, herpes simplex, and syphilis is performed if intrauterine infection or neonatal sepsis and meningitis are suspected. A genetic workup and other metabolic studies are performed if errors of metabolism or other inherited disorders are thought to be present (Merritt & Gallagher, 2018; Neil & Volpe, 2018).

TABLE 15.2

NURSING ASSESSMENT OF SELECTED CRANIAL NERVES IN THE NEWBORN

Nerve	Assessment	Implications
Optic (II)	Blink in response to light (consistent by 28 weeks' gestation) Fixation on object placed approximately 19 cm in front of infant's face (consistent by 32 weeks' gestation) Follows object with eyes and by turning head (consistent by 37 weeks' gestation) Examination of external eye	Visual system intact to the level of the superior colliculi (does not indicate visual cortex function) Presence of vision
Oculomotor (III), trochlear (IV), and abducens (VI)	Funduscopic examination (ophthalmoscope set at 2–4 diopters) Pupillary reactivity (equal and responsive to light; appears by 28 weeks' gestation and consistent by 32 weeks) Doll's eye maneuver (vestibular response; present by 25 weeks' gestation): hold infant in an upright position at arm's length and rotate in both directions	Evaluation of abnormalities (e.g., cataracts, irregularities of size or shape, microphthalmos, or scleral hemangiomas) Normal newborn optic disc is pale or grayish-white; observe for abnormalities (e.g., retinal hemorrhage or lesion) Intact cranial nerve III; unequal or nonresponsive pupils in infants over 32 weeks' gestation are associated with increased ICP or hemorrhage Stimulation of semicircular canals with impulses sent to the brainstem via nerves III, VI, and VII. Normal response is isotonic deviation of the eyes away from the direction of movement; lack of response is associated with brainstem dysfunction or excessive administration of sedatives such as phenobarbital; disconjugate eye movements and some nystagmoid movements occasionally are seen normally during the first 3 weeks
Trigeminal (V)	Elicit the corneal reflex (may not be reliable in newborn) or observe for a grimace on pinprick Elicit sucking and ability of infant to bite down on examiner's finger	Facial sensation (not usually done routinely but may be useful with an infant with facial paralysis) Masticatory power
Facial (VII)	Observe appearance and symmetry of face at rest and during spontaneous and elicited movement	Abnormalities associated with birth injury and cerebral insults
Acoustic (VIII)	Evaluate auditory function by noting response (blink or startle) to sudden loud noise (seen by 28 weeks' gestation) or (in more mature infants) by cessation of movement and turning to sound while in a quiet, alert state	A gross assessment of auditory function; failure of the infant to respond while in a quiet, alert state in a quiet environment on repeated examinations indicates the need for examination of auditory function
Trigeminal (V), facial (VII), glossopharyngeal (IX), vagus (X), and hypoglossal (XII)	Evaluate sucking (V, VII, XII), swallowing (IX and X), and gag reflex (IX and X)	Impairment interferes with feeding and may indicate or be associated with cerebral insult

ICP, intracranial pressure.

Sources: Data from Amiel-Tison, C., & Gosselin, J. (2009). Clinical assessment of the infant nervous system. In M. I. Levene & F. A. Chervenak (Eds.), *Fetal and neonatal neurology and neurosurgery* (4th ed., pp. 128–154). Edinburgh, Scotland: Churchill Livingstone/Elsevier; Volpe J. J. (2018a). Injuries of the extracranial, cranial, intracranial, spinal cord, and peripheral nervous system structures. In J. J. Volpe, T. E. Inder, B. T. Darras, L. S. de Vries, A. J. du Plessis, & J. M. Perlman (Eds.), *Volpe's neurology of the newborn* (6th ed., pp. 1093–1125). Philadelphia, PA: Elsevier; and Volpe, J. J. (2018b). Neurological examination: Normal and abnormal features. In J. J. Volpe, T. E. Inder, B. T. Darras, L. S. de Vries, A. J. du Plessis, J. J. Neil, & J. M. Perlman (Eds.), *Volpe's neurology of the newborn* (6th ed., pp. 191–221). Philadelphia, PA: Elsevier.

TABLE 15.3

CLINICAL MANIFESTATIONS OF CNS DYSFUNCTION

Alteration	Clinical Manifestations
CNS depression	Altered level of consciousness
	Weak, absent cry
	Weak, absent primary reflexes
	Poor feeding
	Decreased activity
	Decreased passive tone
	Decreased active tone
	Altered respirations
Hyperirritability	Sharp, excessive crying
	Hyperactivity
	Exaggerated passive tone
	Hypertonia
	Difficult to console
	Low sensory threshold
Increased ICP	Irritability
	Lethargy
	Increased head circumference
	Palpable sutures, especially squamous
	Bulging, tense fontanelle
	Increased extensor tone of neck
	Downward deviation of eyes
	Vomiting (late)
	Dilated head veins (late)
Seizures	See Table 15.5
Movement alterations	Jitteriness, tremors
	Decerebrate posturing
	Decorticate posturing
	Opisthotonos

(*continued*)

TABLE 15.3

CLINICAL MANIFESTATIONS OF CNS DYSFUNCTION (*continued*)

CNS, central nervous system; ICP, intracranial pressure.

Sources: Data from Amiel-Tison, C., & Gosselin, J. (2009). Clinical assessment of the infant nervous system. In M. I. Levene & F. A. Chervenak (Eds.), *Fetal and neonatal neurology and neurosurgery* (4th ed., pp. 128–154). Edinburgh, Scotland: Churchill Livingstone/Elsevier; Heaberlin, P. D. (2019). Neurologic assessment. In E. P. Tappero & M. E. Honeyfield (Eds.), *Physical assessment of the newborn: A comprehensive approach to the art of physical examination* (6th ed., Chapter 11) [Kindle version]. Santa Rosa, CA: NICU Ink; and Volpe (2018a, b).

GENERAL MANAGEMENT

Management specific to each type of neurologic dysfunction is described in later sections. However, in the nursing care of infants with neurologic dysfunction, common nursing diagnoses and management techniques that must be considered with all infants and their families are included in the following list. Those marked with an asterisk (*) are discussed in other chapters.

1. Alteration in level of consciousness
   - Monitor infant's state, activity level, responsiveness, eye movements, head circumference, and vital signs; also monitor for seizure activity and signs of increased ICP
   - Position infant so as to promote skin integrity, prevent contractures, and reduce ICP (i.e., head in midline and slightly elevated)
   - Monitor fluid and electrolyte status
   - Maintain adequate ventilation and perfusion
   - Implement comfort measures
   - Maintain an appropriate thermal environment
   - Reduce environmental stressors
   - Promote neurobehavioral stability
2. Potential for injury related to trauma or infection
   - Use sterile technique
   - Position infant to prevent contamination of defects or operative sites
   - Monitor for signs of localized infection or neonatal sepsis
   - Handle infant gently
   - Position infant to reduce potential of trauma or contamination
3. Impairment of skin integrity
   - Position infant in alignment and change position regularly
   - Use foam, sheepskin, lambskin, or waterbeds
   - Massage skin gently to stimulate circulation
   - Use appropriate skin care measures
4. Alteration in comfort*

5. Impaired mobility
   - Position infant in alignment and change position regularly
   - Promote skin integrity
   - Use gentle range-of-motion exercises
6. Alteration in thermoregulation*
7. Alteration in nutrition*
8. Promote neurobehavioral organization and development*
9. Altered family processes*
10. Grieving (family)*

NEONATAL SEIZURES

Seizures are the most common neurologic sign during the neonatal period and are more common in the newborn stage than at any other time in childhood. The reported incidence of neonatal seizures is approximately 2 to 4 per 1,000 live term births and 30 to 130 per 1,000 live preterm births (Abend, Jensen, Inder, & Volpe, 2018; Natarajan & Gospe, 2018). Neonatal seizures usually are acute, with a third occurring on the first day and another third on the second day of life, then disappearing within the first few weeks after birth. Perinatal hypoxia-ischemia is generally reported to account for 50% to 60% of all neonatal seizures and is the most common cause of seizures for term newborns; IVH is the most common cause of seizures for preterm newborns (Natarajan & Gospe, 2018; Rennie & Boylan, 2009; Scher, 2012).

Seizures were described by the American Clinical Neurophysiology Society in 2013 as a rhythmic activity lasting 10 seconds with a minimum of 2 μV peak-to-peak (pp) voltage that evolves in quality and subsequently resolves. Events that last less than 10 seconds but have similar characteristics are called brief rhythmic discharges (BRDs). Although BRDs are not considered true seizures, the risk of developing seizures increases when BRDs are observed (Natarajan & Gospe, 2018).

Seizures are not a disease in themselves but a sign of underlying disease processes that have resulted in an acute disturbance within the brain. There is increasing evidence suggesting that these seizures exacerbate brain injury, which increases the necessity for prompt recognition, efficient observation and monitoring methods, and effective therapeutic interventions (Abend et al., 2018; Jensen, 2009; Natarajan & Gospe, 2018; Scher, 2012; Shah, Boylan, & Rennie, 2012). If left untreated, these disorders can lead to permanent damage of the CNS or other tissues. Disease processes associated with seizures in the neonate include primary CNS disorders, hypoxic-ischemic events, systemic diseases, and metabolic insults. Seizure activity may be an acute, recurrent, or chronic phenomenon. Recurrent or continuous seizures increase the risk of neurologic damage from the seizure activity itself (Natarajan & Gospe, 2018; Rennie & Boylan, 2009; Scher, 2012; Shah et al., 2012).

Pathophysiology

Seizures are the result of excessive, synchronous electrical discharge or depolarization in the brain that produces stereotypic, repetitive behaviors. Depolarization and repolarization of the nerves are caused by the movement of sodium and potassium across the cell membrane. The inward migration of sodium ions (Na^+) results in depolarization; repolarization is produced by the outward migration of potassium ions (K^+). These processes require an energy-dependent pump and energy in the form of adenosine triphosphate (ATP). The specific mechanism that causes neonatal seizures is unknown but might be the result of one or more of these mechanisms: (a) disturbances in energy production and the Na^+-K^+ pump, (b) altered neuronal membrane permeability to sodium, and (c) imbalances in excitatory and inhibitory neurotransmitters (Abend et al., 2018; Rennie & Boylan, 2009; Scher, 2012). A disturbance in energy production, with changes in the movement of Na^+ and K^+ across the neuronal membrane, may lead to an imbalance between depolarization and repolarization. The movement of K^+ (repolarization) unbalances the movement of Na^+ (depolarization). Changes in energy production may result from hypoxemia, ischemia, and/or hypoglycemia. Alterations in the permeability of the neuronal membrane to sodium can occur with hypocalcemia. Calcium normally binds with proteins in the cell membrane to inhibit Na^+ movement. A decrease in the availability of calcium would increase inward movement of Na^+ and lead to depolarization. Hypomagnesemia also increases membrane permeability to Na^+, and alkalosis or hyponatremia also leads to seizures through this mechanism. Imbalances in neurotransmitters lead to a relative excess of excitatory neurotransmitter (glutamate or acetylcholine) over inhibitory neurotransmitter (gamma-aminobutyric acid [GABA]) and increases the rate of depolarization. This can occur as a result of an excess of excitatory substance (associated with hypoxemia, ischemia, and hypoglycemia) or a deficiency of inhibitory substance. Pyridoxine deficiency leads to an inhibitory neurotransmitter deficiency by depressing the activity of the enzyme responsible for the synthesis of GABA. Elevated levels of excitatory inhibitors derived from ammonia are seen in infants who have liver dysfunction after severe hypoxic-ischemic events (Abend et al., 2018; Jensen, 2009; Rennie & Boylan, 2009; Scher, 2012).

Biochemical Effects of Seizures

Seizures result in increased energy expenditure, which leads to the following sequence of biochemical events: (a) breakdown of ATP to adenosine diphosphate with release of energy; (b) increased glycolysis, stimulated by adenosine diphosphate, with conversion of glycogen to glucose; (c) increased production of pyruvate, which is used by the mitochondria in ATP production; (d) increased oxygen and glucose consumption; (e) increased production of lactate from pyruvate, stimulated by increased adenosine diphosphate; and (f) lactate/H^+-stimulated local vasodilation, which increases local blood flow and substrate availability (Abend et al., 2018; Rennie & Boylan, 2009; Scher, 2012). The rise in blood pressure associated with seizures also increases cerebral blood flow and substrate availability. Seizures result in a marked decrease in brain glucose concentrations because the cells to replenish ATP supplies use much of the available glucose. Repetitive seizures in the neonate eventually alter brain lipid and protein metabolism and energy metabolism, resulting in a reduction in total brain DNA, RNA, protein, and cholesterol. In animal models, these deficiencies lead to impairment of cellular proliferation, differentiation, and myelination. The effects in the human neonate are unclear but of concern. Brain damage caused by seizure activity could be the result of alterations in protein metabolism or the energy supply, or it could be the result of damage from asphyxia or edema. The extent to which these changes occur in the human newborn with recurrent seizures is controversial; mounting evidence suggests that seizures are associated with less favorable neurobehavioral outcomes (Abend et al., 2018; Scher, 2012).

Seizures in Neonates Compared With Those in Older Children and Adults

Seizures are expressed differently in the neonate than in older individuals because of structural and functional differences in the neonatal brain (Abend et al., 2018; Blackburn, 2018). The peak time

for organizational processes in the brain is from the sixth month of gestation to 1 year after birth; therefore, term and especially preterm infants have relatively immature brain organization. This lack of organization results in an inability to propagate and sustain generalized seizures. For example, the neonate's brain lacks the arborization and synaptic connections (wiring) necessary for a firing neuron to recruit adjacent neurons to fire synchronously. Inadequate organization also leads to a slower response to stimuli (Blackburn, 2009a, 2009b; Volpe, 2008). The lower rate of nerve conduction, limited myelination, and smaller number of connections between neurons alter the threshold for neuron firing and ability to propagate seizures (Abend et al., 2018; Blackburn, 2018; Scher, 2012).

The neonate has increased inhibitory synapses compared with excitatory synapses which may actually be a protective mechanism because it reduces the chance that a generalized seizure will be propagated in the cerebral cortex. As a result, cortical seizures are rare in neonates (Abend et al., 2018; Blackburn, 2018). The newborn has more excitatory (glutamate) than inhibitory neurotransmitters. In addition, GABA, the main inhibitory neurotransmitter in adults, is excitatory in the newborn. The glutamate level is increased (it is needed by the brain for neuronal development and organization); maturation of the inhibitory system is delayed; and the number of NMDA receptors that respond to glutamate is increased (Blackburn, 2018; Rennie & Boylan, 2009). Seizure activity in these infants is more likely to be generated in areas of the brain that are more mature, such as the temporal lobe and subcortical structures, especially in the limbic area. The limbic area, located above the corpus callosum, is one of the oldest parts of the brain in terms of embryologic development. This area is involved with behaviors such as sucking, drooling, chewing, swallowing, oculomotor deviations, and apneic episodes, behaviors typical of those seen with subtle seizures in the neonate (Abend et al., 2018; Blackburn, 2018).

Assessment

Seizures are a clinical manifestation associated with various underlying pathologic processes (Table 15.4), including hypoxia, ischemia, hypoglycemia, hypocalcemia, intracranial hemorrhage, infection (meningitis, congenital viral infections, viral encephalopathy), congenital anomalies of the CNS, and other metabolic disturbances, such as alkalosis, hypomagnesemia, hypernatremia, and hyponatremia. Less common causes of seizures are drug withdrawal from opiates or barbiturates, genetic disorders of amino and organic acid metabolism, kernicterus, hyperviscosity, and local anesthetic intoxication (Abend et al., 2018; Natarajan & Gospe, 2018; Rennie & Boylan, 2009; Scher, 2012).

Seizures can be difficult to recognize in neonates because the clinical manifestations often are subtle and can be associated with other disorders or can involve individual behaviors such as grimacing, startle, sucking, and twitching. Seizures can also occur with minimal or no outward signs, leading to an increasing reliance on EEG or aEEG. Recognition of seizures in the neonatal period requires careful, continuous assessment by the nurse of all infants at risk. Clinical manifestations may include abnormal movements or alterations in tone of the trunk or extremities; abnormal and repetitive facial, oral, tongue, or ocular movements such as blinking, lip smacking, or chewing motions; and increases in blood pressure and apneic events (Abend et al., 2018; Natarajan & Gospe, 2018; Pisani & Pavlidis, 2018; Rennie & Boylan, 2009). Specific examples of each of these are listed in Table 15.5.

Types of Seizures

Various classifications of neonatal seizures are used, some focusing primarily on clinical and behavioral manifestations, others on the presence or absence of echocardiogram correlates (Rennie & Boylan, 2009; Scher, 2012). Increasing evidence supports a combination of clinical categories with electrographical confirmation, especially with the recent advances in digital technology that make it possible to archive and review huge amounts of data generated by bedside video-EEG monitoring (Abend et al., 2018; Pisani & Pavlidis, 2018; Rennie & Boylan, 2009; Scher, 2012). The addition of simultaneous, continuous video-EEG and aEEG (method of displaying one or two channels of compressed and filtered EEG readings) monitoring may refine the diagnosis and management of newborns, with seizure activity categorized within traditional classifications. The aEEG monitoring technique is a relatively easy method of detection of seizure activity and is in use with increasing regularity and reliability for monitoring the neurologic status of infants with HIE (Abend et al., 2018; Bonifacio, Glass, Peloquin, & Ferriero, 2011; Pisani & Pavlidis, 2018; Rennie & Boylan, 2009; Toet & de Vries, 2012).

Determining the etiology of the seizure is important as it will provide the opportunity to administer specific treatment and for prognostic information. Many etiologies may cause neonatal seizures but relatively few etiologies account for the majority of neonatal diagnoses. Seven tertiary care pediatric centers in the United States comprising the Neonatal Seizure Registry consortium collected prospective data related to etiology for 426 newborns with seizures who underwent continuous EEG (cEEG). This study found that 38% of the newborns experiencing seizures related to HIE, 18% with ischemic stroke, 13% with neonatal onset epilepsy, 11% with intracranial hemorrhage, 6% with neonatal genetic epilepsy syndrome, 4% with congenital cerebral malformation, and 3% with benign familial neonatal epilepsy (BFNE). In addition, 59% of the newborn subjects experienced greater than seven electrographic seizures, and 16% developed status epilepticus. There was no significant difference in the number of seizures between preterm and full-term newborns or among the three most common causes of seizure (HIE, ischemic stroke, and intracerebral hemorrhage; Abend et al., 2018).

Traditional clinical seizure classification identifies the following seizure types: subtle, tonic, clonic (multifocal or migratory, and focal), and myoclonic (Abend et al., 2018; Natarajan & Gospe, 2018; Rennie & Boylan, 2009). Subtle seizures are the most common type of seizure seen in neonates, particularly among preterm infants. This type of seizure often is missed because the clinical manifestations may be difficult to recognize and distinguish from other events. The behaviors most commonly seen with subtle seizures are (a) tonic, horizontal deviations of the eyes with or without nystagmoid jerking; (b) repetitive blinking or fluttering of the eyelids; (c) drooling, sucking, or tongue thrusting; and (d) swimming or rowing movements of the arms with occasional bicycling movements of the legs. Apnea may occur but usually is the result of the underlying cause of the seizure in the preterm, rather than of the seizure, and rarely occurs as an isolated seizure event (Abend et al., 2018; Natarajan & Gospe, 2018; Rennie & Boylan, 2009; Scher, 2012).

The most common form of tonic seizure is the generalized tonic seizure, which usually involves tonic extension of all the extremities but sometimes is limited to a single extremity or is manifested by tonic flexion of all limbs. Generalized tonic seizures can be confused with decorticate or decerebrate posturing. Other signs may include eye deviations, apnea, and occasional clonic movements. This type of seizure is the one seen most frequently in preterm infants, especially those with IVH and hypoxic-ischemic insults. Generalized tonic seizures often are accompanied by apnea or decerebrate-type postures, or both. Occasionally, focal tonic seizures may occur, which are characterized by sustained asymmetric posturing of the limbs, trunk, or neck. Focal tonic seizure activity may be difficult to differentiate from voluntary movement

TABLE 15.4

MAJOR CAUSES OF NEONATAL SEIZURES

Cause and Frequency (% of Total)	Usual Age at Onset (Days)	Predominant Type of Seizure
Hypoxic-ischemic injury (38% [Abend et al., 2018]; others 50%–60%)	After 1 or more (often 6–18) hours following birth; 90% in the first 72 hours	Subtle (all), generalized tonic, multifocal clonic
Perinatal stroke (18%); arterial ischemic strokes most frequent; cerebral sinovenous thrombosis		
Hypocalcemia (15%)	Early: 1–3 days; late 4–7 days	Usually focal or multifocal
Neonatal onset epilepsy (13%)		
Neonatal genetic epilepsy syndrome (6%)		
Intracranial hemorrhage (11%)		
IVH	Most within first 3 days; later with late-onset IVH	Subtle progressing to generalized tonic with severe IVH
SAH	2–3	Any type
SDH	1–2	May be focal
Hypoglycemia (10%)	1–3	Usually focal or multifocal
Infections (5%–10%)		
Bacterial meningitis	4–7	Any type; may be tonic
Viral encephalopathy	2–15	Any type
Congenital viral infection	3–7	Tonic, myoclonic
CNS malformations (<5%–10%)	2–10 (often not until several months of age)	Tonic, myoclonic
Drug withdrawal (rare)	3–34	Tonic or myoclonic
Local anesthetic intoxication[a] (uncommon)	Before 1 (1–6 hours after birth)	Tonic

CNS, central nervous system; IVH, intraventricular hemorrhage; SAH, subarachnoid hemorrhage; SDH, subdural hemorrhage.

[a] Caused by accidental injection of local anesthetic into the scalp during placement of paracervical, pudendal, or epidural blocks or during injection of local anesthetics at delivery.

Sources: Data from Abend, N. S., Jensen, F. E., Inder, T. E., & Volpe, J. J. (2018). Neonatal seizures. In J. J. Volpe, T. E. Inder, B. T. Darras, L. S. de Vries, A. J. du Plessis, J. J. Neil, & J. M. Perlman (Eds.), *Volpe's neurology of the newborn* (6th ed., pp. 275–324). Philadelphia, PA: Elsevier; Rennie, J. M., & Boylan, G. B. (2009). Seizure disorders of the neonate. In M. I. Levene & F. A. Chervenak (Eds.), *Fetal and neonatal neurology and neurosurgery* (4th ed., pp. 698–710). Edinburgh, Scotland: Churchill Livingstone/Elsevier; Scher, M. S. (2012). Diagnosis and treatment of neonatal seizures. In J. M. Perlman (Ed.), *Neurology* (2nd ed., pp. 109–141). Philadelphia, PA: Saunders/Elsevier; Volpe (2008);

(Abend et al., 2018; Heaberlin, 2019; Natarajan & Gospe, 2018; Rennie & Boylan, 2009; Scher, 2012).

Clonic seizures may be multifocal or focal. Because multifocal or migratory clonic seizures involve the cortex, they are more characteristic of term infants but occasionally may be seen in older preterm infants. This type of seizure involves rhythmic, jerky clonic movements of one or more limbs that migrate to other parts of the body in a random fashion. Multifocal clonic seizures can be confused with jitteriness. These seizures are associated with diffuse hyperexcitability of the cortex, such as occurs with metabolic derangements (Abend et al., 2018; Natarajan & Gospe, 2018).

Focal clonic seizures are also seen more frequently in term than in preterm infants. This form of seizure is characterized by localized clonic jerking that is usually present in one limb or the face. Focal clonic seizures may be associated with focal traumatic CNS injuries, such as cerebral contusions and infarcts, or may be

TABLE 15.5

CLINICAL MANIFESTATIONS OF SEIZURES IN THE NEONATE

Type of Manifestation	Specific Alterations
Abnormal movement or alterations of tone in the trunk and extremities	Clonic (generalized or multifocal, migratory)
	Altering hemiclonic tonic (single extremity), extension of arms and legs ("decerebrate-like"), extension of legs and flexion of arms ("decorticate-like"), or generalized
	Myoclonic (isolated or general)
	Bicycling movements of legs
	Swimming or rowing arm movements
	Loss of tone with general flaccidity
Facial, oral, and tongue movements	Sucking
	Grimacing
	Twitching
	Chewing, swallowing, yawning
Ocular movements	Tonic horizontal eye deviation
	Staring, blinking
	Nystagmoid jerks
Respiratory manifestations	Apnea (usually preceded or accompanied by one or more subtle manifestations)
	Hyperpneic or stertorous breathing

Sources: Data from Heaberlin, P. D. (2019). Neurologic assessment. In E. P. Tappero & M. E. Honeyfield (Eds.), *Physical assessment of the newborn: A comprehensive approach to the art of physical examination* (6th ed., Chapter 11) [Kindle version]. Santa Rosa, CA: NICU Ink; Jensen, F. E. (2009). Neonatal seizures: An update on mechanisms and management. *Clinics in Perinatology, 36*, 1–20. doi:10.1016/j.clp.2009.08.001; and Scher, M. S. (2012). Diagnosis and treatment of neonatal seizures. In J. M. Perlman (Ed.), *Neurology* (2nd ed., pp. 109–141). Philadelphia, PA: Saunders/Elsevier.

a response to a severe metabolic disturbance or asphyxia and occur in combination with other seizure types (Abend et al., 2018; Heaberlin, 2019; Natarajan & Gospe, 2018; Scher, 2012).

Myoclonic seizures are uncommon in term infants and are rarely seen in preterm infants. These seizures are characterized by single or multiple sudden jerks with flexion of the upper (most common) or lower extremities and occasionally the trunk and neck. Myoclonic seizures are most often seen with inborn errors of metabolism or other metabolic problems (Heaberlin, 2019; Natarajan & Gospe, 2018; Rennie & Boylan, 2009).

Management

Management of neonatal seizures has two goals: (a) to determine and treat the underlying cause of the seizures and (b) to protect the infant from injury during and after the seizure. Determining the cause involves assessment of the perinatal and neonatal history, a physical examination, laboratory evaluation, and other diagnostic studies. Previous events that may indicate the underlying cause include the delivery history, bleeding, birth trauma, hypoxic-ischemic events, exposure to infectious agents and other teratogens, maternal substance abuse, and postbirth illnesses.

The physical examination includes evaluation of the infant's general health and neurologic status. Routine laboratory studies include electrolyte levels; glucose, calcium, magnesium, and blood urea nitrogen (BUN) levels; Hct value; blood gases; and pH. A blood culture and lumbar puncture are also often performed. A lumbar puncture helps to rule out both infection and CNS bleeding. Other laboratory and diagnostic studies may include screening for congenital viral infections, amino acid screening (for inborn errors of metabolism), CT, ultrasonography, MRI, skull radiography, or EEG. The results of a continuous video-EEG can provide information for the prognosis, more so in a term than a preterm infant (Abend et al., 2018; Heaberlin, 2019; Scher, 2012).

Quality and Safety: Seizures must be recognized, seizure activity documented, and the infant protected and supported during and after the seizure. Observing and documenting seizure activity involves noting and recording (a) the time the seizure begins and ends; (b) the body parts involved (e.g., extremities, eyes, head); (c) a description of motor movement, eye deviations, and pupillary reactions; and (d) the infant's respiratory status, color, state, level of consciousness, and postictal status. **Emergency Alert: During the seizure, the infant's airway must be maintained, vital signs monitored, and the infant assessed for adequacy of respiration and heart rate to maintain ventilation and perfusion.** To protect the infant from injury during the seizure, the nurse should not force anything into the infant's mouth or try to restrain the infant's extremities. The nurse should try to turn the infant's head to the side, if possible. After the seizure, the infant's condition should be monitored, and supportive care should be provided so that ventilation, oxygenation, adequate fluids, glucose, and warmth are maintained. The nurse also should assess the infant for signs related to the events that can cause seizure activity in the neonate to help determine the cause of the seizure and prevent additional seizures (Heaberlin, 2019; Scher, 2012).

The overall goal of treatment of neonatal seizures is to prevent long-term brain damage through management of the underlying cause of the seizures and cessation of the clinical and electrical seizure activity (Abend et al., 2018; Natarajan & Gospe, 2018). Treatment of the underlying cause of the seizure is a priority for preventing more seizures and neurologic damage. Continual monitoring of blood gases, acid–base status, serum glucose, and fluid and electrolyte status is important for any infant with seizures. Infants who have seizures, regardless of the cause, require intravenous administration of glucose because seizure activity depletes brain glucose and energy supplies (Abend et al., 2018; Blackburn, 2018; Natarajan & Gospe, 2018). Alterations in oxygenation and acid–base status can occur as a complication of the apnea associated with a seizure or the physiologic consequences of seizure activity. Fluid and electrolyte management should be appropriate to the underlying cause of the seizures. For example, fluids are restricted initially in infants with cerebral edema and perinatal hypoxic-ischemic injury (Abend et al., 2018; Natarajan & Gospe, 2018). Management of intracranial hemorrhage and CNS anomalies is discussed later in this chapter. Management of other conditions, such as hypoxic-ischemic events, metabolic and electrolyte disorders, infections, and drug withdrawal, are discussed in detail in other chapters.

The issues of when to treat with anticonvulsant drugs, which drug or combination of drugs to use, and duration of treatment are controversial (Scher, 2012; Shetty, 2015). Some clinicians favor early, aggressive therapy, whereas others do not because neonatal seizures often abate spontaneously (Shetty, 2015). Recurrent or prolonged seizures require treatment with anticonvulsants to reduce the risk of brain injury. Controversy over what medications to use to provide control of neonatal seizures persists due to the diversity of etiology, complexities of diagnosis, and the limited efficacy of the known anticonvulsants available in treating neonatal seizures (Shetty, 2015). In general, however, the current consensus is that the first-line anticonvulsant used for seizure control in the newborn continues to be phenobarbital; phenytoin (Dilantin) is second-line if seizures persist (Scher, 2012; Shetty, 2015). Other drugs used include fosphenytoin (recommended for IV use over phenytoin) and benzodiazepines such as lorazepam and midazolam (Abend et al., 2018; Natarajan & Gospe, 2018; Rennie & Boylan, 2009; Scher, 2012; Shetty, 2015). Phenobarbital, phenytoin, and fosphenytoin doses may be given incrementally to reach therapeutic blood levels, which then must be monitored carefully to maintain therapeutic effect and prevent toxicity. Refractory seizure may require alternative agents such as clonazepam, lidocaine, carbamazepine, diazepam, valproate, or primidone (Abend et al., 2018; Natarajan & Gospe, 2018; Rennie & Boylan, 2009; Scher, 2012). Recent studies on the use of bumetanide for neonatal seizures have been promising; further research is necessary to provide evidence for efficacy (Pressler et al., 2015).

Length of treatment after seizure activity has been controlled and after the infant has recovered is undefined at this point. Often the duration of treatment is clinically determined by etiology of the seizures, the time taken, and amount of medications required to control the seizure activity. It may range from length of hospitalization to 2 years post discharge, provided there is no further seizure activity or perceived neurologic indication for extending treatment (Abend et al., 2018; Natarajan & Gospe, 2018; Scher, 2012).

Because anticonvulsants can be respiratory or myocardial, and CNS depressants can compete with bilirubin for albumin binding, the infant's cardiorespiratory status, color, and neurologic status are monitored in addition to drug effectiveness. Parent teaching includes helping the family to understand the cause and significance of the seizure or seizures and any diagnostic tests that are planned. Discharge teaching of parents includes recognition of seizure manifestations, care of the infant during and after a seizure, and administration of anticonvulsants (dosage and side effects) if administration of these drugs is to be continued after discharge.

Outcomes

The mortality rate for infants with seizures has declined in recent years, from approximately 33% in the 1990s to 10% reported (range: 7%–16%; Natarajan & Gospe, 2018; Uria-Avellanal, Marlow, & Rennie, 2013). Two-thirds of infants with seizures, especially premature infants and/or those with repeated seizures, have adverse neurologic sequelae, including epilepsy (20%–25%), motor deficits, intellectual disabilities, and subtle deficits, such as learning disabilities or poor social adjustment in teen years. Benign seizures in otherwise healthy infants during the first week have a good prognosis (Natarajan & Gospe, 2018; Uria-Avellanal et al., 2013). Preterm infants tend to recover more rapidly from a seizure than do term infants; however, mortality and later morbidity are higher in preterm infants. The prognosis for infants who have seizures during the neonatal period is influenced by (a) the time of onset, (b) the cause of the seizure, (c) continuous video-EEG results, (d) responsivity to treatment, and (e) the frequency and duration of the seizures (Abend et al., 2018; Inder & Volpe, 2018a; Natarajan & Gospe, 2018; Rennie & Boylan, 2009; Scher, 2012; Uria-Avellanal et al., 2013). Seizure onset less than 48 hours after birth has a poor prognosis, whereas onset after 4 days generally has a good prognosis. Clonic seizures have a better prognosis than the other types. The EEG results appear to be a better prognostic sign in term than in preterm infants (Abend et al., 2018; Natarajan & Gospe, 2018; Scher, 2012).

The poorest prognosis is seen with seizures associated with severe hypoxic-ischemic injury, grade III or grade IV IVH, herpes infection, some bacterial meningitis, and CNS malformations. The best prognosis is seen in infants with seizures secondary to late hypocalcemia, hyponatremia, and uncomplicated subarachnoid hemorrhage (SAH). Other causes have a mixed prognosis. Repeated or prolonged seizures can lead to brain injury by altering cerebral blood flow and delivery of oxygen and nutrients, by depleting brain glucose and energy stores, and by interfering with ventilation (Abend et al., 2018; Inder, Perlman, & Volpe, 2018a; Natarajan & Gospe, 2018).

HYPOXIC-ISCHEMIC ENCEPHALOPATHY

HIE is an injury to the brain caused by oxygen deficit resulting from either systemic hypoxemia (decreased oxygen in blood supply) or ischemia (diminished cerebral blood perfusion) or a combination of the two conditions. The hypoxemia and ischemia may occur simultaneously or sequentially, and it appears from recent evidence that ischemia is the more important of the two oxygen deprivation states in causing the brain injury. In addition, the subsequent reperfusion of the affected brain area has been shown to be the time at which the majority of the injury to the brain occurs. Glucose deprivation also plays a part in the severity of the brain injury (Inder & Volpe, 2018a; McAdams & Traudt, 2018). HIE may occur secondary to prenatal, intrapartum, or postnatal insults in both preterm and term infants. The site of injury varies with maturational changes in the vascular anatomy and metabolic activity of the brain. In the preterm infant younger than 32 to 34 weeks' gestation, hypoxic-ischemic damage usually is associated with germinal matrix hemorrhage/IVH. The incidence of severe forms of HIE has declined markedly as a result of advances in perinatal care. Most perinatal hypoxic-ischemic events are mild with minimal effects. The insult is significant enough to cause transient organ dysfunction in 2 to 5 per 1,000 live births and result in death or significant neurologic sequelae in 1 per 1,000 (Dickey, Long, & Hunt, 2011; Inder & Volpe, 2018a; McAdams & Traudt, 2018; Wachtel & Hendricks-Muñoz, 2011).

Pathophysiology

After 33 to 34 weeks' gestation, blood flow and brain metabolic activity become less prominent in the germinal matrix and periventricular area and shift to the cortical area. Hypoxia and ischemia in older preterm and term infants, therefore, are more likely to damage areas of the peripheral and dorsal cerebral cortex. Five types of lesions have been identified in infants with HIE: (a) selective neuronal necrosis; (b) status marmoratus of the neurons of the basal ganglia and thalamus, with loss of neurons in these areas; (c) parasagittal cerebral injury; (d) PVL (primarily in preterm infants); and (e) focal or multifocal ischemic brain necrosis (Inder & Volpe, 2018a; McAdams & Traudt, 2018).

The primary lesion for the hypoxic injury is neuronal necrosis in the cortices of the cerebrum and cerebellum, with damage to the gray matter at the depths of the sulci. Neurons of the brainstem may also be injured. Areas of necrosis may extend into the white matter and into the gray matter of the basal ganglia. The primary ischemic injury occurs in the posterior portion of the parasagittal region secondary to watershed or border zone infarcts. The border zone is at the junctions of the anterior, middle, and posterior cerebral arteries and the superior and inferior cerebellar arteries. This area is farthest from the major cerebral vessels, which are the source of the blood supply for the brain. Thus, with localized ischemia, such as occurs when the infant has systemic hypotension or hypoperfusion, this area receives the least amount of blood. With hypoxia and systemic hypotension, cerebral perfusion is maintained at first by cerebral vasodilation and redistribution of blood flow to the brain from other organs. If the hypoxia continues, cerebral blood flow is altered; energy is depleted; ischemia and edema develop; and neurophysiologic activity is disrupted. At the cellular level, neurologic injury is caused by energy depletion, accumulation of extracellular glutamate, and activation of glutamate NMDA receptors. This process occurs in two phases. The initial insult and effects of hypoxia lead to hyperpolarization with an influx of sodium, potassium, and water into the cell. This interferes with the cell's ability to produce an action potential, leading to failure of the sodium-potassium pump and cell edema. Calcium moves into the cell via voltage-dependent ion channels opened by the changes in the sodium-potassium pump. This reduces calcium currents and release of neurotransmitters. These events may be protective mechanisms to reduce neuronal excitability and conserve oxygen. However, reperfusion and reoxygenation may lead to buildup of free oxygen radicals and primary neuronal death. If the hypoxia and ischemia persist, NMDA receptors are activated, which further increases intracellular calcium (entering the cell via glutamate-controlled ion channels). More glutamate is released and accumulates to toxic levels. Nitric oxide (NO) is also released and accumulates. NO, which at normal levels promotes vasodilation and increased blood flow, reaches toxic levels, leading to the production of excess free oxygen radicals and further activation of NMDA receptors. NO combines with superoxide free radicals to produce the toxic peroxynitrates, causing further cell damage. This late reperfusion phase (usually beginning 6–12 or more hours after the initial insult) is characterized by hyperexcitability and cytotoxic edema and damage caused by the release of free oxygen radicals and NO, inflammatory changes, and imbalances in inhibitory and excitatory neurotransmitters with secondary neuronal death due to necrosis or apoptosis (Dickey et al., 2011; Inder & Volpe, 2018a; Johnston, Fatemi, Wilson, & Northington, 2011; Sorem, Smith, & Druzin, 2009; Stola & Perlman, 2008). After a hypoxic-ischemic insult, the entire cortex initially may be edematous, and further ischemic damage may occur as a result of compression of the cortex against the skull.

Assessment

Most term infants with HIE demonstrate a characteristic pattern of neurologic findings over the first 72 hours of life, including seizures, altered levels of consciousness, altered tone, altered activity, irregular respirations, apnea, poor or absent Moro reflex, abnormal cry, poor suck, and altered pupillary responses and eye movements. Clinical signs categorizing the severity of HIE have been classified in three stages first by Sarnat and Sarnat (1976) and are summarized in Table 15.6. Stage 1, mild HIE, is characterized by mild depression or hyperalertness, irritability, and sympathetic nervous system excitation (tachycardia, dilated pupils). These infants have a good Moro reflex and deep tendon reflexes and generally are symptomatic for less than 24 hours or so. Infants in Stage 2, moderate HIE, demonstrate lethargy interspersed with brief arousal, decreased tone, altered primary reflexes, and increased parasympathetic tone (bradycardia, decreased pupil size and blood pressure) and may develop seizures. Infants in Stage 3, severe HIE, have varying levels of consciousness initially but then become stuporous or comatose. These infants have depressed deep tendon and Moro reflexes, as well as hypotonia, and most develop seizures. Seizures occur in up to 60% of infants with HIE, with a usual onset at 12 to 14 hours of age. The types of seizures most often seen are multifocal clonic seizures in term infants, although myoclonic clonic and/or subtle seizures may also be seen (Inder & Volpe, 2018a; Johnston et al., 2011; McAdams & Traudt, 2018).

Management

Infants with HIE have multiorgan and multisystem problems that arise from the original hypoxic-ischemic insult (McAdams & Traudt, 2018; Sarkar, Barks, Bhagat, & Donn, 2009; Tagin, Woolcott, Vincer, Whyte, & Stinson, 2012; Zanelli, Buck, & Fairchild, 2011). As a result, management of these infants is complex and requires a coordinated team effort. Acute management of infants with HIE focuses on delivery room resuscitation and stabilization and management of the primary problem and related alterations in the

TABLE 15.6

STAGES OF HYPOXIC-ISCHEMIC ENCEPHALOPATHY

	Stage 1: Mild	Stage 2: Moderate	Stage 3: Severe
Level of consciousness	Hyperalert	Lethargic; obtunded	Stuporous
Pupils	Dilated	Constricted	Variable; unequal
Heart rate	Tachycardic	Bradycardic	Variable
Muscle tone	Normal	Mildly hypotonic	Flaccid
Myoclonus	Present	Present	Absent
Sucking reflex	Weak	Weak; absent	Absent
Salivary secretions	Sparse	Profuse	Absent
Moro embrace reflex	Strong	Weak; incomplete	Absent
Seizures	None	Common; focal or multifocal	Uncommon
Duration of symptoms and recovery	<24 hours	2–14 days	Hours to weeks

Sources: Compiled from Chirinian, N., & Mann, N. (2011). Therapeutic hypothermia for management of neonatal asphyxia: What nurses need to know. *Critical Care Nurse, 31*(3), e1–e12. doi:10.4037/ccn2011873; Inder, T. E., & Volpe, J. J. (2018a). Hypoxic-ischemic injury in the term infant: Clinical-neurological features, diagnosis, imaging, prognosis, therapy. In J. J. Volpe, T. E. Inder, B. T. Darras, L. S. de Vries, A. J. du Plessis, J. J. Neil, & J. M. Perlman (Eds.), *Volpe's neurology of the newborn* (6th ed., pp. 510–563). Philadelphia, PA: Elsevier; McAdams, R. M., & Traudt, C. M. (2018). Brain injury in the term infant. In C. A. Gleason & S. E. Juul (Eds.), *Avery's diseases of the newborn* (10th ed., pp. 897–910). Philadelphia, PA: Elsevier; Sarkar, S., Barks, J., Bhagat, I., & Donn, S. (2009). Effects of therapeutic hypothermia on multiorgan dysfunction in asphyxiated newborns: Whole-body cooling versus selective head cooling. *Journal of Perinatology, 29*, 558–563. doi:10.1038/jp.2009.37; Sarnat, H., & Sarnat, M. (1976). Neonatal encephalopathy following fetal distress: A clinical and electroencephalographic study. Archives of Neurology, 33, 696–705. doi:10.1001/archneur.1976.00500100030012

cardiovascular, pulmonary, gastrointestinal, and renal systems. Prompt identification and treatment of seizures are needed to prevent further alterations in ICP and cerebral blood flow. Management of these infants in relation to neurologic problems focuses on elimination of the cause of the original hypoxia, alleviation of tissue hypoxia, and promotion of adequate cerebral perfusion and brain oxygenation with maintenance of an adequate glucose supply. Inotropic support may be necessary to provide adequate perfusion (Kelen & Robertson, 2010; McAdams & Traudt, 2018; Stola & Perlman, 2008; Wachtel & Hendricks-Muñoz, 2011).

Interventions are directed toward establishing ventilation and adequate perfusion and preventing or minimizing hypotension, hypoxia, acidosis, rapid alterations in cerebral blood flow and systemic blood pressure, and severe apneic and bradycardic episodes. Hyperoxia is also avoided because this state can result in cerebral vasoconstriction and diminished perfusion. The infant's neurologic status is continually monitored and documented, as are oxygenation, temperature, and blood pressure (Stola & Perlman, 2008; Wachtel & Hendricks-Muñoz, 2011). HIE must be differentiated from other neurologic dysfunctions caused by trauma, infection, or CNS anomalies. An extensive workup to define the type, extent, and location of the injury may include cranial ultrasonography, brainstem auditory evoked potentials, MRI, EEG, and measurements of cerebral blood flow, ICP, and the creatinine kinase level (Gunny & Lin, 2012; Stola & Perlman, 2008; Tao & Mathur, 2010; Toet & de Vries, 2012; Wachtel & Hendricks-Muñoz, 2011; Walsh, Murray, & Boylan, 2011).

Other parameters that are monitored are the serum and urinary electrolyte levels and osmolality; BUN, serum creatinine, and glucose levels; and fluid and electrolyte balance. These infants are at risk for hypocalcemia secondary to release of excessive phosphorus from the breakdown of ATP that occurred to produce energy; the need for energy arises in response to the stress induced by perinatal hypoxic-ischemic injury. The excess phosphorus is also related to the use of bicarbonate to correct acidosis induced by these events. After hypoxic-ischemic events, an infant is at risk for hypoglycemia as a result of depletion of stores from high energy; therefore, provision of adequate glucose for energy and interventions to reduce energy expenditure are important. Fluid status and intake and output are monitored to prevent fluid overload and to reduce localized increases in pressure; fluids are restricted, although the effectiveness of this intervention has not been evaluated with clinical trials. Fluid management is critical not only for treating the cerebral edema but also for managing the alterations in renal function and problems such as acute tubular necrosis that frequently accompany moderate to severe stages of HIE (Liao, Xu, Ding, & Huang, 2018; Stola & Perlman, 2008; Wachtel & Hendricks-Muñoz, 2011).

Induced mild hypothermia has been shown to provide neuroprotection and reduce the extent of tissue injury and is increasingly the treatment of choice for infants greater than or equal to 36 weeks' gestation with moderate-to-severe HIE (Bonifacio, Gonzalez, & Ferriero, 2012; Inder & Volpe, 2018a; Laptook, 2012; McAdams & Traudt, 2018; Pfister & Soll, 2010; Rutherford et al., 2010; Stola & Perlman, 2008). Potential mechanisms for these effects with

hypothermic therapy include inhibition of glutamate release, reduction in cerebral metabolism, and preservation of high-energy phosphates. Additional neuroprotective mechanisms include decreases in intracellular acidosis and lactic acid accumulation, preservation of endogenous antioxidants, reduction in NO production, decrease in protein kinase inhibition, improved protein synthesis, reduction in leukotriene production, minimization of blood–brain barrier disruption, reduced brain edema, and apoptosis inhibition (Hoehn et al., 2008; Inder & Volpe, 2018a; Liao et al., 2018; Pfister & Soll, 2010; Stola & Perlman, 2008). Techniques studied include either selective head cooling or whole-body cooling to attain mild systemic hypothermia of 32°C to 34°C core body temperature (Barks, 2008; Hoehn et al., 2008; Inder & Volpe, 2018a; Kelen & Robertson, 2010; Laptook, 2012; McAdams & Traudt, 2018; Stola & Perlman, 2008). Infants are assessed to determine whether hypothermia criteria are met before the cooling regimen is initiated. Current criteria used to determine if a newborn is a candidate for hypothermia are (a) term infants ≥36 weeks' gestation without major congenital anomalies, intrauterine growth restriction (IUGR; ≤1,800 g), or known chromosomal anomaly; (b) admitted at less than or equal to 6 hours of age to the neonatal intensive care unit (NICU); (c) assessed to be in Stage 2 moderate HIE, or Stage 3, severe HIE by neonatologist and/or pediatric neurologist (Gancia & Pomero, 2011; Hoehn et al., 2008; Inder & Volpe, 2018a). The cooling regimen continues for 72 hours and is begun as soon as possible after birth, by 5.5 to 6 hours postbirth and optimally before seizure activity is noted (Bonifacio et al., 2011, 2012; Hoehn et al., 2008; Inder & Volpe, 2018a; Laptook, 2012; Liao et al., 2018; McAdams & Traudt, 2018; Stola & Perlman, 2008). Within 6 hours of birth is a therapeutic window demonstrated in sheep between insult and further cell death for neuroprotective interventions; early hypothermia studies indicate that cooling may be less effective if started after onset of seizures or in infants with most severe EEG changes before therapy (Gancia & Pomero, 2011; Gluckman et al., 2005; Gunn et al., 2008; Inder & Volpe, 2018a; Liao et al., 2018; McAdams & Traudt, 2018).

Hypothermia therapy has multisystem effects in addition to the effects resulting from HIE (Table 15.7; Battin et al., 2009;

TABLE 15.7

POTENTIAL PHYSIOLOGIC EFFECTS OF HYPOTHERMIA BY SYSTEMS WITH MEDICAL AND NURSING INTERVENTIONS

System	Potential Physiologic Effects	Medical and Nursing Interventions
Neurologic	Decreased cerebral blood flow	Observe for seizure activity
	Decreased cerebral metabolic rate	Monitor infant's state of arousal
	Amplitude and frequency	EEG, cEEG with video; aEEG
Respiratory	Decreased respiratory drive	Monitor respiratory rate, effort; may need intubation, ventilation
	Increased pulmonary vascular resistance	Monitor systemic blood pressure
	Increased CO_2 and O_2 solubility	Monitor blood gases (preferably arterial)
	Decreased CO_2 production and O_2 consumption	Adjust assisted ventilation as needed to prevent hypercarbia, hypoxia
	Increased pH by 0.0016 for every 1°C decrease in temperature	Monitor saturations with pulse oximetry to prevent hypoxia
	Decreased minute ventilation to preserve normal $Paco_2$	
Cardiovascular	Decreased heart rate by 14–60 bpm	Monitor continuous cardiorespiratory monitoring
	Increased systemic vascular resistance	Monitor invasive arterial blood pressure
	Decreased cardiac output	Observe changes in perfusion status, urine output
	Decreased intravascular volume	Maintain blood pressure within parameters with vasopressors, boluses
	Potential for ECG changes: prolonged PR, QRS, QT	Monitor cardiac strips; obtain ECG as needed

(*continued*)

TABLE 15.7

POTENTIAL PHYSIOLOGIC EFFECTS OF HYPOTHERMIA BY SYSTEMS WITH MEDICAL AND NURSING INTERVENTIONS (*continued*)

System	Potential Physiologic Effects	Medical and Nursing Interventions
Renal	Decreased renal perfusion and glomerular filtration rate	Monitor fluid intake, urine output
	Impaired salt and water reabsorption	Obtain electrolytes every 4–8 hours as needed
	Diuresis	
	Potential for hypokalemia with increased intracellular uptake	Maintain normal potassium level
	Potential for hyperkalemia during rewarming	
	Potential for decreased calcium, magnesium, phosphorus	
Gastrointestinal	Decreased intestinal blood flow	Provide parenteral nutrition
*		Begin enteral nutrition cautiously after rewarming; monitor for intolerance
Hematologic	Decreased platelet count; thrombocytopenia	Monitor platelet count every 6–12 hours as indicated
	Increased activation and aggregation (clumping)	
	Increased PT, PTT	Monitor PT, PTT every 12–24 hours as indicated
Immunologic	Impaired neutrophil release and function	Monitor CBC with differential at least every 24 hours
	Decreased leukocyte chemotaxis	
	Decreased phagocytosis and killing	

aEEG, amplitude-integrated EEG; CBC, complete blood count; cEEG, continuous EEG; PT, prothrombin time; PTT, partial thromboplastin time.

Sources: Compiled from Chirinian, N., & Mann, N. (2011). Therapeutic hypothermia for management of neonatal asphyxia: What nurses need to know. *Critical Care Nurse, 31*(3), e1–12. doi:10.4037/ccn2011873; Lista, G., Castoldi, F., Cavigioli, F., Bianchi, S., Fontana, P., & La Verde, A. (2011). Ventilatory management of asphyxiated infant during hypothermia. *Journal of Maternal-Fetal and Neonatal Medicine, 24*(Suppl. 1), 67–68. doi:10.3109/14767058.2011.607615; Reynolds, R., & Talmage, S. (2011). "Caution! Contents should be cold": Developing a whole-body hypothermia program. *Neonatal Network, 30*(4), 225–230. doi:10.1891/0730-0832.30.4.225; Selway, L. D. (2010). State of the science: Hypoxic-ischemic encephalopathy and hypothermic intervention for neonates. *Advances in Neonatal Care, 10*(2), 60–66. doi:10.1097/ANC.0b013e3181d54b30; Toet, M. C., & de Vries, L. S. (2012). Amplitude-integrated EEG and its potential role in augmenting management within the NICU. In J. M. Perlman (Ed.), *Neurology* (2nd ed., pp. 263–284). Philadelphia, PA: Saunders/Elsevier; Vandertak, K. (2009). Cool competence. The nursing challenges of therapeutic hypothermia. *Journal of Neonatal Nursing, 15*(6), 200–203. doi:10.1016/j.jnn.2009.07.011; Verklan, M. T. (2009). The chilling details: Hypoxic-ischemic encephalopathy. *Journal of Perinatal and Neonatal Nursing, 23*(1), 59–68. doi:10.1097/01.JPN.0000346221.48202.7e; Wachtel, E. V., & Hendricks-Muñoz, K. D. (2011). Current management of the infant who presents with neonatal encephalopathy. *Current Problems in Pediatric and Adolescent Health Care, 41*(5), 132–153. doi:10.1016/j.cppeds.2010.12.002; and Zanelli, S., Buck, M., & Fairchild, K. (2011). Physiologic and pharmacologic considerations for hypothermia therapy in neonates. *Journal of Perinatology, 31*(6), 377–386. doi:10.1038/jp.2010.146V

Glass, 2010; Liao et al., 2018; Lista et al., 2011; Reynolds & Talmage, 2011; Selway, 2010; Vandertak, 2009; Verklan, 2009). The infants undergoing a cooling regimen, either selective head cooling or whole-body cooling, require optimal care and attention at the bedside; this intervention is only being done in tertiary NICU settings (Barks, 2008; Liao et al., 2018; Reynolds & Talmage, 2011; Selway, 2010; Zanelli et al., 2011). Delays in transport are critical and should be avoided. Induced hypothermia is not recommended either prior to or during transport. Care should be taken that the infants not become hyperthermic with core temperatures greater than 37°C (Glass, 2010; Hoehn et al., 2008; Pfister & Soll, 2010).

Fluctuations in systemic blood pressure with increased ICP and altered cerebral hemodynamics can occur as a result of caregiving or environmental stress; therefore, developmentally supportive care of these infants to reduce stress is essential. As the infant recovers, opportunities for sensory experiences are an important part of care. These experiences can be introduced

slowly, as the infant can tolerate them without becoming stressed and overloaded. Physiologic and neurologic status is monitored and documented at regular intervals. The infant is observed for changes in level of consciousness, tone, and activity and for evidence of seizures. Seizures are recognized and treated promptly to prevent further injury. Positioning and skin care are important, especially for hypoactive, obtunded, or comatose infants. Physiologic and clinical effects and supportive measures for infants treated with hypothermia are summarized in Table 15.7.

Parents need initial and continuing support in dealing with their infant's critical illness; the lack of infant responsiveness if the infant is hypoactive, stuporous, or comatose; the possibility of death; and the implications for later neurologic deficits. Parent teaching focuses on promoting an understanding of the infant's health status and care and providing anticipatory guidance regarding changes in the infant's state, as well as the outcome (Long & Brandon, 2007; Selway, 2010). The parents need to be shown how to interact with and care for their infant in a developmentally appropriate manner, with the goal of promoting opportunities for interaction while minimizing stressful events. The nurse can model this type of care for the parents and provide anticipatory guidance in the ways the infant's needs and care will change as the baby matures. Parents can also be involved in devising and implementing a developmental plan of care for their infant (Gudsnuk & Champagne, 2011; Sullivan, Perry, Sloan, Kleinhaus, & Burtchen, 2011).

Outcomes

The prognosis, which varies with the extent and severity of the insult and the resulting brain injury, ranges from perinatal death to severe neurologic impairment to minimal or no sequelae. Specific sequelae may not be apparent for several months or longer. Some infants make a significant recovery, although the rate and degree of recovery vary. MRI or CT can be used to assess the location, degree, and extent of the injury (Epelman, Daneman, Chauvin, & Hirsch, 2012; Gunn et al., 2008; Gunny & Lin, 2012; Inder & Volpe, 2018a; Liao et al., 2018; Lodygensky, Menache, & Hüppi, 2012; Lori et al., 2011; McAdams & Traudt, 2018). Sequelae of HIE in term infants are related to the site of injury (e.g., the cortex) and include intellectual disabilities, microcephaly, cortical blindness, hearing deficits, and epilepsy. Generally, infants with mild HIE do well. Infants with moderate HIE or severe HIE have a higher mortality rate and later cognitive and motor problems (de Vries & Jongmans, 2010; Gunn et al., 2008; Inder & Volpe, 2018a; McAdams & Traudt, 2018; Wyatt et al., 2007).

The advent of hypothermia therapy as a treatment modality appears to have improved the general outcome, especially for infants with Stage 2 moderate HIE. Most human studies report beneficial effects of hypothermia therapy in terms of improved survival and outcome with no significant adverse effects for infants with Stage 2 moderate HIE (Bonifacio et al., 2012; Gunn et al., 2008; Inder & Volpe, 2018a; Liao et al., 2018; McAdams & Traudt, 2018; Rutherford et al., 2010; Volpe, 2008). A recent meta-analysis comparing head cooling with total body cooling technique showed both to be effective treatments for moderate-to-severe HIE, resulting in reduction in the risk of death or major neurodevelopmental disability at 18 months, particularly for infants with moderate HIE (Tagin et al., 2012). Guillet et al. (2012) reported subtle cognitive and motor neurological disabilities at school age (7–8 years) follow-up of the CoolCap study. The authors also reported support for long-term predictive value of a favorable outcome at 18 months of age.

BRAIN INJURY IN PRETERM INFANTS

Preterm infants are particularly vulnerable to brain injury, with the greatest prevalence of neurologic alterations seen in very low birth weight infants. These infants are at increased risk for cognitive, behavioral, motoric, vision, hearing, attentional, and socialization problems (Blackburn, 2016; Neil & Volpe, 2018; Symes, 2016). Major disabilities (cognitive, motor, vision, hearing) are seen in 6% to 8% of infants from 1,501 to 2,000 g birth weight, increasing to 14% to 17% at 1,001 to 1,500 g and 20% to 30% in infants weighing less than 1,000 g at birth (Symes, 2016). Cognitive dysfunction continues into school age and adulthood (15%–25% in those born at <1,500 g and over 50% in those <750 g; Back, 2015; Back & Miller, 2018; Symes, 2016). Reductions in cerebral white and gray matter growth are seen in these infants (Back & Miller, 2018; Penn, Gressens, Fleiss, Back, & Gallo, 2016; Symes, 2016).

The major etiologic events leading to brain injury in preterm infants are a combination of pathophysiologic events leading to specific injuries and an increased susceptibility to injury due to their stage of brain development leading to interruption or disruption of brain development. The relative contributions of altered or delayed maturation versus specific injury are unclear (Penn et al., 2016). Developmentally, preterm infants are vulnerable to alterations in brain maturation and injury because they are born "at a time of peak brain growth, synaptogenesis, developmental regulation of specific receptor populations, and central nervous system organization and differentiation" (Symes, 2016, p. 1157). Exposure to pain and stress, opioids and other pharmacologic agents, and the NICU environment may also influence brain development and maturation in preterm infants (Blackburn, 2018; Penn et al., 2016).

The main pathophysiologic events leading to brain injury in preterm infants are hypoxia-ischemia and inflammation/infection (Inder, Perlman, & Volpe, 2018b). The primary lesions seen in these infants are germinal matrix hemorrhage–IVH, which may include periventricular hemorrhagic infarction (PVHI) and posthemorrhagic hydrocephalus, WMI (including PVL, often accompanied by gray matter damage with neuronal and axonal damage), and cerebellar injury (Back & Miller, 2018; Juul, Fleiss, McAdams, & Gressens, 2018; Kinney & Volpe, 2018a; Volpe et al., 2011). PVL accompanied by neuronal and axonal abnormalities has been referred to as the encephalopathy of prematurity and is the most common brain injury currently seen in preterm infants (Kinney & Volpe, 2018a; Volpe et al., 2011).

Prevention of brain injury in preterm infants is a complex process that begins in the perinatal period with prevention of preterm birth, perinatal asphyxia, and birth trauma (Blackburn, 2016; Juul et al., 2018). Neuroprotective strategies for preterm infants include use of antenatal glucocorticoids, antenatal magnesium sulfate to reduce the risk of cerebral palsy, delayed cord clamping, and neonatal skin to skin contact (kangaroo care; Doyle, Crowther, Middleton, Marret, & Rouse, 2009; Hirtz et al., 2015; Juul et al., 2018; Silva, Barros, Pessoa, & Guinsburg, 2016). Currently under investigation are the use of melatonin and erythropoietin (Juul et al., 2018). Nursing management after birth involves recognition of factors that increase the risk of brain injury, implementation of strategies to reduce these risks, and supportive care (Blackburn, 2016).

Germinal Matrix-Intraventricular Hemorrhage

Germinal matrix-intraventricular hemorrhage (GMH/IVH, or, most commonly, IVH) is the most common type of intracranial hemorrhage seen in the neonatal period (Back & Miller, 2018; Inder et al., 2018b; Takenouchi & Perlman, 2012). IVH is seen

almost exclusively in preterm infants, particularly those weighing less than 1,500 g. Decreasing gestational age increases the risk and severity of IVH. Incidence of IVH in premature infants less than 1,500 g has remained fairly stable for the past decade at 15% to 25% (Back & Miller, 2018; Ballabh, 2014; Inder et al., 2018b; Takenouchi & Perlman, 2012). However, the risk of IVH and severe IVH is higher in more immature infants, especially those with birth weights less than 750 g (Inder et al., 2018b). The major risk factors for IVH in the neonate are prematurity and hypoxic events interrelated with the anatomic and physiologic processes that make the periventricular site particularly vulnerable. IVH occurs but is uncommon after 35 to 36 weeks' gestation because of the involution of the subependymal GM and alterations in cerebral blood flow patterns that occur after this time. Any perinatal or neonatal event that results in hypoxia or alters cerebral blood flow or intravascular pressure increases the risk of IVH (Inder et al., 2018b). IVH is classified by the location and severity of the hemorrhage. Several classifications are available (Back & Miller, 2018). Using Volpe's system, a grade I or slight hemorrhage is characterized by isolated GM hemorrhage; a grade II or small hemorrhage by IVH with normal ventricular size; and a grade III or moderate hemorrhage IVH with ventricular dilation and hemorrhage in greater than 50% of the ventricle (Inder et al., 2018b). PVHI or severe hemorrhage (also referred to as grade IV) involves both intraventricular and brain parenchyma hemorrhage IVH (Back & Miller, 2018; Inder et al., 2018b).

Pathophysiology. The neuropathophysiology of IVH involves a complex interaction of intravascular, vascular, and extravascular factors. In infants of less than 28 to 32 weeks' gestation, the hemorrhage generally arises from the subependymal GM at the head of the caudate nucleus near the foramen of Monro. On those rare occasions when IVH occurs in term infants, bleeding usually arises from the choroid plexus rather than from the GM (Inder et al., 2018b). The GM includes the tissue underlying the ependymal wall of the lateral ventricles. In many preterm infants, the hemorrhage begins as a microvascular event in the GM and is confined to the subependymal area. In the rest, the original hemorrhage ruptures into the lateral ventricles and then into the third and fourth ventricles. The blood eventually collects in the subarachnoid space of the posterior fossa, often extending into the basal cistern (see Figure 15.1; Back & Miller, 2018; Ballabh, 2014). Rupture of the hemorrhage from the GM into the ventricles may serve a protective function by decompressing the hemorrhagic area and reducing further tissue destruction. Progressive ventricular dilation may occur as the result of obstruction of CSF flow by an obliterative arachnoiditis or as the result of blood clots at the level of the aqueduct of Sylvius or the foramen of Monro. With severe hemorrhages (PVHI), blood may also be found in the periventricular white matter, with parenchymal lesions seen in 10% to 15% of very low birth weight infants with an increased risk of adverse neurodevelopmental outcomes (Inder et al., 2018b). These parenchymal lesions are differentiated from PVL in that the circulatory disturbance is venous (vs. arterial in PVL), hemorrhagic (uncommon in PVL), and asymmetric with a single large cyst (vs. more symmetrical findings with multiple small cysts with PVL; Inder et al., 2018b).

The neuropathological consequences of IVH include (a) destruction of the GM and its glial precursor cells, including oligodendrocytes and late migrating GABAergic neurons; (b) infarction and necrosis of periventricular white matter; and (c) posthemorrhagic hydrocephalus (Back & Miller, 2018; Inder et al., 2018b) that alters cerebral brain development, myelination, and axonal maturation (Inder et al., 2018b). Infants with IVH may also have PVL. However, PVL is usually a consequence of hypoxic-ischemic injury and thus may not be a result of the IVH (Inder et al., 2018b).

Intravascular Factors. Intravascular hemodynamic factors play a prominent role in the pathogenesis of IVH. These factors include distribution of blood to the periventricular region, pressure-passive cerebral blood flow, and venous hemodynamics. The stages of CNS development characteristic of preterm infants born at less than 32 to 33 weeks' gestation increase the risk of hemorrhage in the periventricular area (Blackburn, 2018).

Periventricular Blood Flow. The subependymal GM is a transient structure that begins to thin after 14 weeks, then increases to become the site of neuron and glia proliferation, and then involutes during the third trimester (Inder et al., 2018b). This is the site where neuroectodermal cells that serve as precursors for neurons (primarily before about 24 weeks' gestation) and glial cells develop. These cells subsequently migrate to their eventual locus in the cerebral cortex. Processes involved in the proliferation, differentiation, and migration of these cells result in an area that is highly vascularized and metabolically active. Before 32 weeks' gestation, a significant portion of the total cerebral blood flow goes to the periventricular GM, primarily to support neuroblast and glioblast mitotic activity and migration. Any factor that increases cerebral blood flow can result in overperfusion of the periventricular region. After 32 to 34 weeks' gestation, cell proliferation and migration decline; the GM becomes less prominent and receives a smaller proportion of the cerebral blood supply. After this time, the greater proportion of blood flow is to the rapidly differentiating cerebral cortex (Back & Miller, 2018; Blackburn, 2016; Inder et al., 2018b).

Cerebral Autoregulation. The blood vessels of the brain normally are protected from marked alterations in flow by autoregulatory processes. If cerebral autoregulation is intact, the arterioles constrict or dilate to maintain a constant cerebral blood flow despite fluctuations in systemic blood pressure. Hypoxia and hypoxemia in the neonate alter cerebral autoregulation. This can lead to a pressure-passive system in which cerebral blood flow varies directly with arterial pressure. Subsequent alterations in systemic blood pressure or cerebral blood flow, or both, are transmitted directly to the brain and, in particular, to the area receiving the greatest proportion of cerebral blood flow, that is, the fragile, thin-walled vessels of the GM in preterm infants. Thus, rapid fluctuations in systemic blood pressure or cerebral blood flow (i.e., moving from increased to decreased flow and vice versa) may increase the risk of vessel rupture (Back & Miller, 2018; Fyfe, Yiallourou, Wong, & Horne, 2014; Inder et al., 2018b). Altered hemodynamics with fluctuations in blood flow can occur with positive pressure ventilation, rapid volume expansion, hypercapnia, and possibly reduced Hct and blood glucose values. Increased systemic blood pressure and, potentially, cerebral blood flow also can occur with caregiving events, such as handling, suctioning, and chest physical therapy (Blackburn, 2016; Inder et al., 2018b; Takenouchi & Perlman, 2012).

Venous Hemodynamics. Increased venous pressure, arising from events such as myocardial failure or positive pressure ventilation, can also be transmitted directly to the capillaries of the GM. These events can impede cerebral venous return, leading to stasis and venous congestion, which then lead to increased venous pressure and vessel rupture. The point of vulnerability in the venous drainage system of the brain is at the level of the foramen of Monro and the caudate nucleus (the usual site of IVH). At this location, a U-shaped turn occurs in the venous drainage system where the confluence of the thalamostriate, terminal, and choroidal veins forms the internal cerebral vein, which empties into the great vein

of Galen. This results in a sharp change in the direction of blood flow and predisposes to turbulent venous flow with stasis and thrombus formation and an area vulnerable to increased intravascular pressure (Inder et al., 2018b). In addition, the pliable skull of the preterm infant can easily be deformed, obstructing the major venous sinuses and increasing venous pressure.

Vascular Factors. The capillary bed of the GM is immature and has large, irregular, thin-walled vessels, a feature that increases its vulnerability to rupture. The capillary walls thicken with increasing gestational age. The fragility of these vessels is due partly to the lack of thickness and strength of the basement membrane, limitations in pericytes that provide basement membrane support, and the lack of collagen and smooth muscle (Ballabh, 2014; Blackburn, 2016; Walsh, Inder, & Volpe, 2017). With migration of the neuronal and glial cells and their derivatives, the GM undergoes involution. The immature capillary bed is remodeled into the definitive, mature capillary. The epithelial cells of these capillaries are dependent on oxidative metabolism and thus are easily injured by hypoxic events. This characteristic increases the likelihood of leakage or rupture if transmural pressure increases. Because these vessels require an adequate supply of oxygen to maintain their functional integrity, decreased cerebral blood flow can lead to hypoxic-ischemic injury. These vessels are also susceptible to ischemia because they tend to lie in the vascular border zone, or "watershed" area. Both increased and decreased cerebral blood flow, therefore, can be involved in the pathogenesis of IVH (Ballabh, 2014; Blackburn, 2018; Inder et al., 2018b).

Extravascular Factors. The capillary bed of the highly vascularized GM is embedded in gelatinous material deficient in supportive mesenchymal elements, thus providing poor support for the fragile blood vessels. In addition, excessive fibrinolytic activity occurs in the periventricular area. As a result, a small initial bleed may not clot off and be localized, but rather may continue to enlarge and rupture into the ventricles, or the cerebral parenchyma, or both (Ballabh, 2014; Inder et al., 2018b; Walsh et al., 2017).

Assessment. Perinatal events associated with fetal and neonatal hypoxia include maternal bleeding, fetal distress, perinatal hypoxic-ischemic injury, prolonged labor, maternal infection, preterm labor, and abnormal presentation. Neonatal hypoxic events, such as respiratory distress, apnea, and hypotension, further increase the risk of IVH. Events associated with impairment of venous return, increased venous pressure, or both, include assisted ventilation, high positive inspiratory pressure, prolonged duration of inspiration, continuous positive airway pressure (CPAP), and air leak. Venous pressure can also be increased by compression of the infant's skull during vaginal delivery, application of forceps, and use of constricting head bands. Rapid administration of hypertonic solutions (e.g., sodium bicarbonate and glucose), rapid volume expansion, hypernatremia, hypercarbia, caregiving interventions, and environmental stress can increase cerebral blood flow. Hypercarbia causes cerebral vasodilation, thus increasing blood flow. Hypertonic solutions given rapidly or in a large bolus alter osmotic gradients between the brain and the blood. Repeated or prolonged seizures raise the blood pressure and can lead to hypoxia (Blackburn, 2018; Inder et al., 2018b; Walsh et al., 2017).

The clinical manifestations of this disorder often are nonspecific and are not well correlated with later sonographic evidence of bleeding. Therefore, a high index of suspicion, along with careful monitoring, is important for infants at risk. The diagnosis is generally made by cranial ultrasound to determine the presence and severity of IVH and the progression of the hemorrhage, as well as to monitor later complications such as PVL, progressive ventricular dilation, and posthemorrhagic hydrocephalus (Back & Miller, 2018; Takenouchi & Perlman, 2012; Walsh et al., 2017). Although CT scans and MRI can also be used, cranial ultrasound is preferred since it does not involve ionizing radiation and is easily done at the bedside (Inder et al., 2018b).

More than 90% of infants with IVH bleed within the first 72 hours after birth; less than 5% develop after 4 to 5 days. Extension of the hemorrhage may be seen during the first few days (Back & Miller, 2018; Ballabh, 2014). Late hemorrhages after a few days or weeks are seen primarily in preterm infants with severe, prolonged respiratory problems. A new hemorrhage or an extension of a previous one may develop in these infants. IVH may also develop before birth in some infants (Inder et al., 2018b).

The signs and symptoms of IVH are often nonspecific and subtle. Clinical signs may include a full anterior fontanelle, changes in activity level, and decreased tone. Other clinical signs associated with IVH are impaired visual tracking, increased tone of the lower limbs, hypotonia of the neck, and brisk tendon reflexes (Back & Miller, 2018; Inder et al., 2018b).

Besides a declining Hct or failure of the Hct to increase after transfusion, laboratory evidence suggestive of IVH involves CSF findings indicative of hemorrhage: increased red blood cell levels, increased protein levels, decreased glucose levels, and xanthochromia (often a later finding and caused by increased protein). Extremely low CSF glucose levels, or hypoglycorrhachia, can be found several days to a week (usually 5–15 days) after the hemorrhage in some infants.

The patterns of clinical manifestations seen in individual infants vary widely and range from silent or subtle to catastrophic. At one end of the continuum are infants with IVH who have only silent, subependymal bleeding with no or minimal clinical signs. This is the most common and often discovered during routine ultrasound screening. Other infants may demonstrate clinical manifestations, including alterations in level of consciousness or stupor, hypotonia, abnormal eye movements or positions, and altered mobility. These infants generally survive. Later developmental outcome varies, depending on the severity of the hemorrhage (Back & Miller, 2018; Inder et al., 2018b).

Catastrophic deterioration usually involves major hemorrhages that evolve rapidly over several minutes or hours. **Emergency Alert: Clinical findings include stupor progressing to coma, respiratory distress progressing to apnea, generalized tonic seizures, decerebrate posturing, fixation of pupils to light, and flaccid quadriparesis.** This clinical presentation is associated with a declining Hct value, bulging fontanelle, hypotension, bradycardia, temperature alterations, hypoglycemia, and syndrome of inappropriate antidiuretic hormone. Infants with catastrophic hemorrhages have a high mortality rate and, if they survive, a poor prognosis for later development (Back & Miller, 2018; Inder et al., 2018b).

Management of GM/IVH. Management of IVH involves prevention of hemorrhage in infants at risk, acute care of infants with current bleeding, pharmacologic therapies, and management of posthemorrhagic ventricular dilation. Routine ultrasound screening of infants at risk for IVH can identify infants with silent bleeding or bleeding associated with nonspecific, subtle symptoms. Prevention or risk reduction begins in the perinatal period, with the prevention of preterm birth, perinatal hypoxic-ischemic injury, and birth trauma. Administration of antenatal glucocorticoids to enhance fetal lung maturation is associated with a decreased incidence of IVH, perhaps due to improved cardiovascular stability (Back & Miller, 2018; Blackburn, 2018; Inder et al., 2018b).

Postbirth prevention and risk reduction must begin immediately at birth. Activities include resuscitation by a trained NICU team and interventions to prevent or reduce hypoxic or ischemic events; to prevent rapid changes in cerebral blood flow, to avoid both hypocarbia and hypercarbia fluctuations in systemic blood pressure, and hyperosmolarity; and to prevent or minimize

fluctuations in ICP. By identifying these vulnerable infants, interventions can be instituted to prevent new bleeding or extensions of existing hemorrhage. Continual assessment of fetal and neonatal oxygenation and perfusion is important so that subtle alterations can be recognized and clinicians can intervene early to prevent cerebral hyperperfusion and stabilize cerebral blood flow and pressures. Prompt resuscitation at birth minimizes hypoxemia and hypercarbia, which can alter cerebral autoregulation. Hypertonic solutions and volume expanders are administered slowly, with careful monitoring of vital signs and color. Activities that can increase ICP or cause wide swings in arterial or venous pressure are avoided or minimized when possible, especially during the first 72 hours of life. Because seizures can alter cerebral blood flow and ICP, they must be recognized promptly and treated (Back & Miller, 2018; Inder et al., 2018b; Takenouchi & Perlman, 2012).

Acute treatment of infants with IVH involves providing physiologic support by maintaining oxygenation, perfusion, normothermia, and normoglycemia. Physical manipulations, handling, and environmental stressors are minimized to reduce the risk of hypoxia and of fluctuations in arterial blood pressure and cerebral blood flow. The infant's position is also important. The head is positioned in a neutral position in the midline or to the side, without flexing the neck. The head of the bed can be elevated slightly. The Trendelenburg position is avoided. Vital signs, blood pressure, tone, activity, and level of consciousness are monitored frequently. The care of infants with progressive ventricular dilation is discussed in the section on hydrocephalus. Developmental interventions, such as containment or swaddling during aversive procedures such as endotracheal suctioning, may promote greater physiologic stability during these procedures and a more rapid return to baseline (Bissinger & Annibale, 2014; Blackburn, 2016, 2018; Kling, 1989; Owens, 2005; Pitcher, Schneider, Drysdale, Ridding, & Owens, 2011). Specific interventions are listed in Table 15.8.

Since IVH generally occurs in the first few days after birth, IVH prevention bundles have been developed and implemented for the first 48 to 72 hours in many units to minimize activities that increase intracranial pressure or lead to alterations in venous and arterial pressure or to hypoxemia and promote neutral head positioning (Christ et al., 2015; de Bijl-Marcus, Brouwer, de Vries, & van Wezel-Meijler, 2017; Malusky & Donze, 2011).

TABLE 15.8

NURSING CARE TO REDUCE THE RISK OF GERMINAL MATRIX HEMORRHAGE/INTRAVENTRICULAR HEMORRHAGE AND OTHER BRAIN INJURY IN PRETERM INFANTS

Intervention	Rationale
Position the infant with the head in the midline (neutral alignment) and the head of the bed slightly elevated.	ICP is lower with the head in the midline and the head of the bed elevated 30°.
	Turning the head sharply to the side causes obstruction of the ipsilateral jugular vein and can increase ICP.
Avoid tight, encircling phototherapy masks.	Pressure on the occiput can increase ICP by impeding venous drainage.
Avoid rapid fluid infusions for volume expansion and rapid infusion of hypertonic solutions such as glucose. (a) Know the normal BP for the infant's weight and age. (b) If the infant is not hypovolemic, suggest dopamine therapy to maintain BP.	Rapid increases in intravascular volume can rupture the capillaries in the germinal matrix, and this risk may be even greater with a history of hypoxia and hypotension. Even modest, abrupt increases in BP may cause IVH.
Monitor BP diligently. Inform physician if with a fluctuating pattern in the arterial pressure tracing.	The blood flow velocity in the anterior cerebral artery is reflected by the pattern of the simultaneously recorded arterial BP.
Monitor closely for signs of pneumothorax, including: (a) Increase in mean BP, especially increases in diastolic BP (early) (b) Tachycardia (early) (c) Hypotension and bradycardia (late) (d) Changes in breath sounds (e) Diminished arterial oxygen pressure (Pao_2) (f) Increased arterial carbon dioxide pressure ($Paco_2$) (g) Shift in cardiac point of maximum impulse	Pneumothorax may precede IVH. The sum of hemodynamic changes caused by pneumothorax is flow under increased pressure in the germinal matrix capillaries. Changes in vital signs can be early indicators of pneumothorax.
Maintain temperature in neutral thermal range.	Hypothermia has been associated with IVH.
Suction only as needed.	Even brief suctioning episodes (20 seconds) can increase cerebral blood flow velocity, BP, and ICP and reduce oxygenation.

(*continued*)

TABLE 15.8

NURSING CARE TO REDUCE THE RISK OF GERMINAL MATRIX HEMORRHAGE/INTRAVENTRICULAR HEMORRHAGE AND OTHER BRAIN INJURY IN PRETERM INFANTS (*continued*)

Intervention	Rationale
Avoid interventions that cause crying. (a) Consider long-term methods of achieving venous access to avoid frequent venipuncture. (b) Critically evaluate all manipulations and handling. (c) Use analgesics for stressful procedures.	Crying can impede venous return and increase cerebral blood volume.
Reduce pain and stress (a) Regular assessment and monitoring of pain (b) Minimize numbers of painful procedures (c) Implement pharmacologic and nonpharmacological pain reduction therapies (d) Monitor the NICU physical and caregiving environment and reduce stressors	Pain and stress may alter neurodevelopment and impair cortical and white matter development. Exposure to repeated pain may alter pain circuitry and responsivity.
Maintain blood gas values within a normal range. (a) Use continuous noninvasive monitoring of oxygenation. (b) Adjust the fractional concentration of oxygen in inspired gas (Fio_2) as needed to maintain the transcutaneous oxygen pressure ($Tcpo_2$) or pulse oximeter values within desired range. (c) Avoid interventions that cause hypoxia.	Hypoxia and excessive hypercapnia are associated with the development of IVH. These events increase cerebral blood flow and may impair the neonate's already limited ability to autoregulate the cerebral blood flow. Hypoxia can injure the germinal matrix capillary endothelium.

BP, blood pressure; ICP, intracranial pressure; IVH, intraventricular hemorrhage; NICU, neonatal intensive care unit.

Sources: Adapted from Bissinger, R. L., & Annibale, D. J. (2014). *Golden hours: Care of the very low birth weight infant.* Chicago, IL: The National Certification Company; Blackburn, S. (2016). Brain injury in preterm infants: Pathogenesis and nursing implications. *Newborn and Infant Nursing Reviews, 16*(1), 8–12. doi:10.1053/j.nainr.2015.12.004; Kling, P. (1989). Nursing interventions to decrease the risk of periventricular-intraventricular hemorrhage. *Journal of Obstetric, Gynecologic, & Neonatal Nursing, 8*, 462–470. doi:10.1111/j.1552-6909.1989.tb00497.x; Owens, R. (2005). Intraventricular hemorrhage in the premature neonate. *Neonatal Network, 24*(3), 55–71. doi:10.1891/0730-0832.24.3.55; Penn, A. A., Gressens, P., Fleiss, B., Back, S. A., & Gallo, V. (2016). Controversies in preterm brain injury. *Neurobiology of Disease, 92*(Part A), 90–101. doi:10.1016/j.nbd.2015.10.012; and Pitcher, J. B., Schneider, L. A., Drysdale, J. L., Ridding, M. C., & Owens, J. A. (2011). Motor system development of the preterm and low birthweight infant. *Clinics in Perinatology, 38*(4), 605–625. doi:10.1016/j.clp.2011.08.010.

Few randomized controlled trials of the effects of neutral head positioning on the incidence of IVH and data are inconclusive (de Bijl-Marcus et al., 2017; Malusky & Donze, 2011; Romantsik, Calevo, & Bruschettini, 2017).

Pharmacologic therapies have been tried prophylactically to reduce the incidence of hemorrhage, to prevent more severe bleeding and/or neurologic damage, or both. Research findings have been inconsistent for most of these therapies (Inder et al., 2018b). For example, prophylactic indomethacin has been reported to reduce the risk of IVH in some, but not all, studies (Inder et al., 2018b).

Parent care involves recognition and discussion of parental concerns about their infant's immediate and long-term prognosis and teaching regarding IVH, as well as its implications and management. The parents need to be shown how to interact with and care for the infant at risk for IVH in a developmentally appropriate manner, with the goal of promoting opportunities for interaction while minimizing stressful events. The nurse can model this type of care for parents and provide anticipatory guidance in ways in which the infant's needs and care will change as the baby matures. Parents can also be involved in devising and implementing a developmental plan of care for their infant to reduce pain and environmental stressors.

Management of Progressive Ventricular Dilation. Because progressive posthemorrhagic ventricular dilation can develop, infants with a history of IVH are followed with serial cranial ultrasonography. Approximately 25% develop a slow, progressive ventricular dilation; 25% develop a nonprogressive dilation; 50% do not develop ventricular dilation (Inder et al., 2018b). Posthemorrhagic hydrocephalus develops after birth at varying times after the initial insult, usually in the first 4 to 8 weeks (Back & Miller, 2018). Head size can increase without increases in ICP (normopressive hydrocephalus) because of the neonate's soft, malleable skull and open sutures and fontanelle. A tense fontanelle may be noted when the infant is placed in an upright position when the fontanelle is typically soft. Progressive ventricular dilation initially may cause compression and damage to the cortex without causing any change in head size and may be apparent only on ultrasound. Signs of increased ICP (e.g., bulging anterior fontanelle, setting-sun sign, dilated scalp veins, and widely separated sutures) tend to be later findings. In most infants, the ventricular dilation occurs slowly, without increased ICP. Ventricular growth spontaneously arrests in approximately 65% (Inder et al., 2018b). The remaining infants continue to demonstrate ventricular dilation and increased ICP.

The initial treatment for normopressive hydrocephalus may be observation because in many infants, ventricular growth arrests spontaneously without therapy. Progressive ventricular dilation with increasing ICP is managed with a ventriculoperitoneal shunt or, if the infant is too ill or too small for surgery, with temporary ventricular drainage (Back & Miller, 2018). A ventriculoperitoneal shunt is the shunt of choice in infants and children because this type is easy to insert, revise, and uncoil as the infant grows. One

end of a radiopaque catheter is placed in the lateral ventricle, usually on the right side, and the other end is placed in the peritoneal cavity. The catheter contains a one-way valve that is palpable on the side of the head near the ear. The shunt may need multiple revisions during childhood for growth and for malfunctioning. Major complications of ventriculoperitoneal shunts are infection and obstruction. Too-rapid drainage of CSF immediately after insertion of the shunt can lead to herniation of the brain or subdural hematoma.

Quality and Safety: After surgery, the infant is positioned on the side opposite the shunt, with the head of the bed flat or slightly elevated (15–30°) to prevent rapid loss of CSF and decompression (Joseph, Killian, & Brady, 2017). The position can be rotated to supine every few hours to prevent skin breakdown. The skin should be kept clean and dry. Once the site has healed, infants may be placed on a donut on the affected side (Joseph et al., 2017). Pressure to the shunt valve should be applied only if ordered by the surgeons (Joseph et al., 2017). Infants with a shunt are observed for signs of localized or systemic infection, ileus, signs of peritonitis, and shunt obstruction. Obstruction of the shunt leads to accumulation of CSF, enlargement of the head, and signs of increased ICP. Infection of the shunt may appear as localized redness or drainage around the incision, temperature instability, altered activity, or poor feeding. Fluid status and intake and output are monitored, and the infant is observed for signs of dehydration from too-rapid loss of CSF. Signs of too-rapid decompression include a sunken fontanelle, agitation or restlessness, increased urine output, and electrolyte abnormalities (Joseph et al., 2017).

Parent teaching before discharge includes care of the infant and shunt, especially positioning and skin care. Parents must be comfortable in handling and caring for their infant before discharge. They should know the signs of shunt malfunction, increased ICP, infection, and dehydration. Continuing follow-up care of the infant and parental support are important. Parents may be referred to parent groups for peer support.

Outcomes. The severity and extent of the hemorrhage and the presence of associated problems (e.g., respiratory distress syndrome, perinatal hypoxic-ischemic injury, and sepsis) influence mortality and morbidity. Infants with a history of IVH are also at risk for developing posthemorrhagic ventricular dilation, which may be normopressive or associated with increased ICP. Infants with small or mild hemorrhages survive and generally have a good outcome, with a low incidence of major neurologic sequelae and posthemorrhagic ventricular dilation. However, these infants may have a higher risk of neurodevelopmental issues than infants without IVH (Back & Miller, 2018). Mortality and the risk of progressive ventricular dilation is increased in infants with moderate hemorrhages and still higher in infants with severe hemorrhages, especially infants <750 g birth weight (Inder et al., 2018b). Although infants with severe hemorrhages tend to have significant motor and cognitive deficits, some seem to escape significant long-term sequelae. The incidence of neurologic sequelae ranges from 15% to 25% in infants with moderate hemorrhage to 50% in infants with grade III hemorrhage and 75% in infants with PVHI (Inder et al., 2018b). Sequelae include cerebral palsy, developmental delay, sensory and attention problems, learning disorders, and hydrocephalus (Takenouchi & Perlman, 2012; Walsh et al., 2017).

White Matter Injury in Preterm Infants

WMI and its associated neuronal and axonal alterations is the most common severe neurologic insult seen in preterm infants (Kinney & Volpe, 2018a; Volpe et al., 2011). White matter hypoxic-ischemic injury involves both cystic and noncystic focal necrotic lesions as well as diffuse WMI with damage to the premyelinating oligodendrocytes, astrogliosis, and microglial infiltration (Back & Miller, 2018; Kinney & Volpe, 2018a). This injury is referred to as PVL. Leukomalacia refers to change in the brain's white matter reflective of softening. Focal cystic necrotic lesions are seen in less than 5% of infants at 24 to 32 weeks' gestation; the more common diffuse noncystic lesions associated with disturbances in myelination are seen on MRI in about one-third of infants at 24 to 32 weeks' gestation accounting for 25% of survivors (Miller & Back, 2017; Neil & Volpe, 2018). WMI often is associated with IVH, but it is a separate lesion that may also occur in the absence of IVH. IVH may contribute to the development of PVL via increased formation of free radicals (Inder et al., 2018b). PVL is a symmetric, nonhemorrhagic, usually bilateral lesion caused by ischemia from alterations in arterial circulation. Time of onset is variable; however, the time of peak vulnerability is prior to 32 weeks' gestation.

WMI is often accompanied by secondary alterations in the brain characterized by axonal and neuronal alteration that may include damage to the thalamus, basal ganglia, cerebral cortex, subplate neurons, and cerebellum, which together are referred to as the encephalopathy of prematurity (Back & Miller, 2018; Kinney & Volpe, 2018a; Neil & Volpe, 2018). Encephalopathy of prematurity is characterized by "multifaceted gray and white matter lesions in the preterm brain that reflect acquired and developmental factors in combination" (Kinney & Volpe, 2018a, p. 389). This results in decreased volume of the cerebral cortex, cerebral white matter, alterations in the basal ganglia and thalamus, and altered thalamic and gyral development (Kinney & Volpe, 2018a). Risk factors include any event during the prenatal, intrapartum, or postbirth periods that results in cerebral ischemia; this includes asphyxia, IVH, hypoxia, hypercarbia, hypotension, cardiac arrest, and infection (in which blood flow is diminished by the action of endotoxins; Miller & Back, 2017).

Pathophysiology. PVL begins with ischemic necrosis of the white matter dorsal and lateral to the external angles of the lateral ventricles, especially in the border zone area, but may extend into the cortical white matter. The border zone is the area farthest from the original source of the cerebral blood supply and thus is most susceptible to ischemic damage from diminished cerebral blood flow (Back & Volpe, 2018). Pathologic changes begin with patchy areas of focal ischemic coagulation that may occur as early as 5 to 8 hours after the initial hypoxic-ischemic insult. This is followed within a few days by proliferation of macrophages and astrocytes, along with endothelial and glial infiltration. Later changes include thinning of the white matter and liquefaction in the central portion of the necrotic area, as well as cavitation, cystic changes, and decreased myelination (Back & Volpe, 2018; Miller & Back, 2017).

The pathogenesis of WMI involves the interaction of three maturation-dependent factors: (a) immature vascular supply to the white matter that reduces oxygen delivery to vulnerable areas of the brain; (b) impairments in cerebral autoregulation, leading to pressure-passive cerebral circulation; and (c) vulnerabilities of the premyelinating oligodendrocytes to damage from reactive oxygen and nitrogen species (free radicals), glutamate, adenosine, and cytokines (Back & Miller, 2018; Volpe et al., 2011). Damage to the premyelin-producing oligodendrocytes leads to release of cytokines (indicating an inflammatory process), glutamate, and free radicals. Oligodendrocyte development and survival are impaired, leading to hypomyelination with subsequent motor, cognitive, and behavioral neurodevelopmental problems. Axonal damage and disruption also occur. Perinatal infection and an inflammatory response with release of proinflammatory cytokines are also thought

to play a prominent role in the pathogenesis of PVL, with potentially potentiating effects of hypoxia and inflammation (Back & Volpe, 2018; Volpe et al., 2011).

Assessment. WMI is multifactorial and arises from a compilation of prenatal or postnatal insults, or both. Risk factors include factors leading to hypoxia-ischemia (fetal metabolic acidosis, respiratory distress syndrome, cardiac insufficiency from a large patent ductus arteriosus, sepsis, and congenital heart disease) and hypotension and inflammation (intrauterine infection, necrotizing enterocolitis, and neonatal sepsis; Miller & Back, 2017; Neil & Volpe, 2018). Often, no clinical findings are specific to WMI or PVL during the first weeks of life unless the damage is severe. Cranial ultrasonography can identify infants at risk for, or who have, early signs of WMI, although ultrasound is not as sensitive in the diagnosis of PVL as it is with IVH. MRI can identify changes early and is especially useful with noncystic and diffuse WMI as well as neurodevelopmental prognosis (Kinney & Volpe, 2018a; Lodygensky et al., 2012; Neil & Volpe, 2018). Infants at risk for WMI should undergo serial cranial ultrasound examinations and again at discharge and with later follow-up. MRI may be of benefit for ongoing follow-up, especially for infants with severe damage with the increased association of neuromotor abnormalities and developing ventricular enlargement (Kinney & Volpe, 2018a; Lodygensky et al., 2012). As the infant matures, neurologic and motor deficits become apparent.

Management. Prevention strategies include prevention of preterm birth, use of antenatal glucocorticoids, prompt stabilization and resuscitation at birth to maintain adequate ventilation, perfusion, and oxygenation (Blackburn, 2016; Neil & Volpe, 2018). Initial management focuses on recognizing and treating the primary insult and its attendant complications and preventing further hypoxic-ischemic damage and inflammation (Blackburn, 2018; Gano, 2016). This involves preventing or minimizing hypotension, hypoxia, acidosis, and severe apneic and bradycardic episodes (Neil & Volpe, 2018). HUS and MRI are used serially to diagnose WMI/PVL and to follow its progression in infants at risk. Later management involves care related to residual problems, such as spastic diplegia and hydrocephalus. Nursing interventions focus on acute management of the primary problem and supportive care for the infant and parents. Nurses have a major role in identifying signs of hypoxia and ischemia and instituting interventions to prevent further ischemic damage. These interventions are similar to those described earlier and in Table 15.8. Environmental stressors may increase the risk for development of IVH and subsequent PVL or may cause associated developmental problems. Developmental and environmental interventions, therefore, are important aspects of nursing care.

Parents need initial and continuing support in dealing with their infant's illness and the risk of later neurologic problems. Parent teaching focuses on promoting an understanding of the infant's health status and care and providing anticipatory guidance and follow-up care. The parents should be shown how to interact with and care for their infant in a developmentally appropriate manner to foster parent–infant interaction and to promote infant organization and development. The nurse can model this type of care for the parents, collaborate with parents in identifying stressors and soothing strategies, and provide anticipatory guidance as the infant's needs and care change.

Outcomes. Infants with WMI usually survive. Those who die in the neonatal period usually do so from the original hypoxic, hemorrhagic, or infectious insult rather than from WMI/PVL per se. Infants with WMI are at higher risk for later developmental problems including cognitive deficits, language impairment, attentional dysfunction, cerebral visual impairment, and autism (Mwaniki, Atieno, Lawn, & Newton, 2012; Neil & Volpe, 2018). These infants are also at risk for spastic diplegia, especially those with multifocal cystic lesions around the lateral ventricles. In infants with spastic diplegia, descending fibers from the motor cortex cross the affected area around the ventricles. Because the leg motor fibers are closest to the ventricles, spastic diplegia of the leg is the most common sequela. With extension of the damage, arm involvement with spastic quadriplegia may occur. Infants with diffuse WMI are more likely to develop visual, cognitive, and neurobehavioral impairments (Takenouchi & Perlman, 2012).

Cerebellar Injury in Preterm Infants

The cerebellum is one of the later structures to mature, with critical developmental events occurring at the end of the second and beginning of the third trimester, accompanied by a rapid growth spurt from 24 weeks through the third trimester and birth (Blackburn, 2016; Limperopoulos, du Plessis, & Volpe, 2018). The cerebellum is important for the development of cognitive, learning, language, behavior, and motor function; it functions as a node in the distribution of neural networks with interconnections with the thalamus and parietal and prefrontal cortex, integrates sensory information, and is important in socialization skills (Blackburn, 2016; Brossard-Racine, du Plessis, & Limperopoulos, 2015; Fumagalli et al., 2015). Since the cerebellum undergoes rapid growth and complexity, and critical developmental processes during the time preterm infants are in the NICU, especially those who are very low birth weight, they are at risk for cerebellar injury (Blackburn, 2016; Brossard-Racine et al., 2015; Haines, Wang, & Pierson, 2013; Limperopoulos et al., 2018). These injuries may alter motor and language development and cognitive, socio-emotional, and behavioral function, and increase the risk of attentional and autism spectrum disorders (Blackburn, 2016; Brossard-Racine et al., 2015; Fumagalli et al., 2015; Limperopoulos, 2010; Limperopoulos et al., 2018).

Mechanisms proposed for the alterations seen in the cerebellum in very low birth weight infants include: (a) direct injury (usually due to cerebral hemorrhage) leading to atrophy and reduced growth of cerebellum; (b) indirect cerebellar injury or underdevelopment associated with cerebral injury; and (c) impaired cerebellar development, without evidence of direct or indirect injury, due to unknown causes (Blackburn, 2018). Cerebellar underdevelopment and hemorrhage are seen primarily in infants born at less than 28 weeks. These infants may have bilateral, usually symmetric, decrease in cerebellar volume. The exact etiology of cerebellar hemorrhage in preterm infants includes factors similar to that of GMH/IVH, including pressure-passive cerebral blood flow, increased venous pressure, fragility of the cerebellar germinal matrix blood vessels, and vasoocclusive injuries (Blackburn, 2018; Fumagalli et al., 2015; Limperopoulos et al., 2018). Cerebellar injury may occur concurrently with PVL or IVH.

BIRTH INJURIES

Traumatic injury to the central or peripheral nervous system can occur during the perinatal or postnatal period. Most of these injuries happen during the intrapartum period and may occur with perinatal hypoxic-ischemic events. Perinatal events most frequently associated with birth injury include midforceps delivery, shoulder dystocia, low forceps delivery, birth weight exceeding 3,500 g, and second stage of labor lasting longer than 60 minutes. The incidence of injury has declined markedly in recent years as a result of improvement in obstetrical care and increased use of cesarean

sections for abnormal presentations. However, birth injuries can also arise from trauma during a cesarean section or resuscitation. Injuries that occur before the intrapartum period usually are caused by compression or pressure injuries from an unusual fetal position. The risk of injury to the central or peripheral nervous system is greater with malpresentation (especially breech), prolonged or precipitate labor, prematurity, multiple gestation, shoulder dystocia, macrosomia, and instrumental delivery. The most prevalent types of injury to the nervous system are extracranial hemorrhage, intracranial hemorrhage, skull fractures, spinal cord injury, and peripheral nerve injury (Hoppe & Benedetti, 2018; Volpe, 2018a).

Extracranial Hemorrhage

Caput succedaneum and cephalohematoma are the most common types of birth injury, as well as the most benign. Caput succedaneum is characterized by soft, pitting, superficial edema that is several millimeters thick and overlies the presenting part in a vertex delivery. This edematous area lies above the periosteum and thus crosses suture lines. The edema consists of serum or blood, or both. Infants with caput succedaneum may also have ecchymosis, petechiae, or purpura over the presenting part. Caput succedaneum occurs in infants after a spontaneous vertex delivery or after the use of a vacuum extractor. This type of extracranial hemorrhage requires no care other than parent teaching regarding its cause and significance. It resolves within a few days after birth with no sequelae. Cephalohematoma occurs in 1.5% to 2.5% of newborns (Hoppe & Benedetti, 2018; Walker, 2018). It involves subperiosteal bleeding, usually over the parietal bone but possibly over other cranial bones. Cephalohematoma usually is unilateral but can be bilateral. This type of hemorrhage is seen most often in males, after the use of forceps, after a prolonged, difficult delivery, and in infants born to primiparas. The characteristic finding is a firm, fluctuant mass that does not cross the suture lines. The mass often enlarges slightly by 2 to 3 days of age. Approximately 5% of infants with unilateral and 18% with bilateral cephalohematomas have a linear skull fracture underlying the mass (Hoppe & Benedetti, 2018; Walker, 2018). In rare cases an infant may have a subdural or SAH.

Caput succedaneum and cephalohematoma over the occipital bone must be differentiated from encephalocele. In contrast to extracranial hemorrhage, an encephalocele is characterized by pulsations, increased pressure (tenseness) with crying, and the appearance of a bony defect on radiographic studies (Heaberlin, 2019; Volpe, 2018a). Infants with a cephalohematoma generally have no symptoms. Management includes parent teaching and monitoring for the development of hyperbilirubinemia (Watchko, 2009). Occasionally an infant with a large cephalohematoma becomes anemic. These infants should also be monitored for symptoms of intracranial hemorrhage or skull fracture. Generally, cephalohematomas resolve between 2 weeks and 6 months of age, and most resolve by 8 weeks. Calcium deposits occasionally develop, and the swelling may remain for the first year.

Subgaleal Hemorrhage. Subgaleal, or subaponeurotic, hemorrhage is the most serious form of extracranial hemorrhage in newborns (Hoppe & Benedetti, 2018; Schierholz & Walker, 2010; Volpe, 2018a; Walker, 2018). Subgaleal hemorrhage occurs in 4 per 10,000 spontaneous vaginal deliveries and 59 per 10,000 vacuum-assisted deliveries. The incidence is also increased with precipitous deliveries, macrosomia, and severe dystocia, and with failed vacuum deliveries requiring forceps. Use of soft silastic cups (rather than the rigid hard cup) with vacuum extractors is associated with fewer scalp injuries, although the soft cups are more likely to fail (Volpe, 2018a; Waller, Gopalani, & Benedetti, 2012). Mortality is 17% to 25%; however, if the infant survives the hemorrhage and does not develop HIE, the hemorrhage usually resolves in 2 to 3 weeks and outcomes are good (Hoppe & Benedetti, 2018; Inder & Volpe, 2018b; Volpe, 2018a; Walker, 2018).

Traction or application of intense shearing forces to the scalp pull the aponeurosis from the vault and rupture large emissary veins. Blood collects in a large potential space between the galea aponeurotica and the periosteum of the skull through which the large emissary veins pass (Schierholz & Walker, 2010; Volpe, 2018a). The area is called a potential space because it is not present until blood separates the galea aponeurotica from the periosteum of the skull. This space can quickly expand to accommodate 260 to 280 mL of blood. Total newborn blood volume is 80 to 100 mL/kg, so this volume may be more than the entire blood volume of some newborns (Schierholz & Walker, 2010; Volpe, 2018a).

Subgaleal hemorrhage is a clinical emergency. These infants usually present at birth or within a few hours after birth (Bonifacio et al., 2012; Hoppe & Benedetti, 2018; Schierholz & Walker, 2010; Volpe, 2018a). Clinical findings include a firm, ballotable head mass that crosses sutures and fontanelles (often extending from the orbital ridge, around the ears to the neck) and increases in size after birth. Each centimeter of enlargement is estimated to be equivalent to 40 mL of blood loss (Hoppe & Benedetti, 2018; Schierholz & Walker, 2010; Volpe, 2018a). The mass mimics edema and shifts with head repositioning. Infants usually show signs of pain on manipulation of the scalp or head. Infants may present with a rapidly falling Hct, anemia, hypovolemia, pallor, hypotension, tachycardia, tachypnea, hypotonia, and other signs of shock (Bonifacio et al., 2012; Hoppe & Benedetti, 2018; Schierholz & Walker, 2010; Volpe, 2018a). Management includes rapid recognition, cardiovascular and respiratory monitoring, administration of blood and volume expanders, and control of bleeding (Hoppe & Benedetti, 2018; Schierholz & Walker, 2010; Volpe, 2018a).

Other Types of Intracranial Hemorrhage

In addition to IVH, several other clinically important types of intracranial bleeding can occur in the neonate, including primary subarachnoid hemorrhage (SAH), subdural hemorrhage (SDH), and intracerebellar hemorrhage. These types of hemorrhage arise from trauma or hypoxia during the perinatal period.

Primary SAH. Primary SAH is the most prevalent form of intracranial hemorrhage in neonates and the least clinically significant for most infants. SAH occurs in both preterm and term infants but is more common in preterm infants. SAH may occur alone (primary SAH) or as a secondary event with other forms of intracranial hemorrhage. For example, with IVH, blood moves into the subarachnoid space via the fourth ventricle (Inder et al., 2018b; Levene & de Vries, 2009; Neil & Inder, 2018).

Pathophysiology. Primary SAH consists of bleeding into the subarachnoid space that is not secondary to subdural or intraventricular bleeding. In neonates, the source of the bleeding is venous blood; in older children and adults, SAH usually involves arterial blood. With primary SAH, blood leaks from the leptomeningeal plexus, bridging veins, or ruptured vessels in the subarachnoid space (Inder et al., 2018a; Levene & de Vries, 2009). This type of hemorrhage is associated with trauma or asphyxia. Trauma that causes increased intravascular pressure and capillary rupture is the underlying causal event in most term infants with SAH. In preterm infants, SAH usually is the result of asphyxial events. Factors that place an infant at risk for SAH include birth trauma, prolonged labor, difficult delivery, fetal distress, and perinatal hypoxic-ischemic events (Inder et al., 2018a; Levene & de Vries, 2009; Neil & Inder, 2018).

Assessment. Three clinical presentations have been described for infants with SAH (Inder et al., 2018a). The most common is a preterm infant with a minor SAH. These infants are asymptomatic. The hemorrhage is discovered accidentally, for example, during a lumbar puncture as part of a sepsis workup. With the second type of clinical presentation, term or preterm infants may show isolated seizure activity at 2 to 3 days of age, or preterm infants occasionally may present with apnea. Between seizures, the infant appears and acts healthy ("well baby with seizures"). Infants in both of these groups survive and usually do well developmentally. The third type of clinical presentation involves infants with a massive SAH that has a rapid and fatal course. This presentation is rare and often is associated with both a severe asphyxial event and birth trauma. Blood in the CSF on lumbar puncture indicates the possibility of SAH, but true hemorrhage must be distinguished from a bloody tap. MRI and CT also can help confirm the diagnosis; ultrasonography is unreliable with SAH (Inder et al., 2018a; Levene & de Vries, 2009).

Management. Management of these infants begins with efforts to prevent or reduce the risk of trauma and hypoxia during the perinatal period, so as to reduce the risk of development of SAH. Infants with SAH are observed for seizures and other neurologic signs during the early neonatal period. Nursing care is primarily supportive and includes maintenance of oxygenation and perfusion and provision of warmth, fluids, and nutrients. Nursing management also involves helping the parents to understand the basis for, and cause and prognosis of, SAH, as well as the care of their infant.

Outcomes. Generally, infants with SAH survive, and asymptomatic infants do well. Up to half of symptomatic infants with severe, sustained traumatic or hypoxic injury with further damage to the CNS have neurologic sequelae (Inder et al., 2018a; Levene & de Vries, 2009). Hydrocephalus occasionally develops in infants with a history of SAH as a result of obstruction of CSF flow by adhesions. These infants should undergo repeat ultrasonographic examinations to monitor ventricular dilation.

Subdural Hemorrhage. SDH is the least common of the hemorrhages seen in newborns; however, recognition of this hemorrhage is important as immediate intervention for large SDH can be lifesaving (Inder et al., 2018a). The incidence of SDH has declined markedly as a result of improvements in obstetrical care. This decrease has been particularly notable in term infants (Inder et al., 2018a; Levene & de Vries, 2009). Risk factors include precipitous, prolonged, or difficult delivery, use of midforceps or high forceps, prematurity, cephalopelvic disproportion, and macrosomia. SDH is seen more often in infants born to primiparas, possibly because of the more rigid birth canal. Infants with abnormal presentations (e.g., breech, foot, brow, or face) are also at higher risk for SDH (Inder et al., 2018a; Neil & Inder, 2018; Waller et al., 2012).

Pathophysiology. SDH in newborns is almost always caused by trauma during the perinatal period. Unilateral or bilateral bleeding occurs between the dura and the arachnoid. The bleeding occurs over the cerebral hemispheres or posterior fossa with or without lacerations of the tentorium or falx cerebri (see Figure 15.1). The cerebral hemispheres are the most common site for SDH. Bleeding usually occurs over the temporal convexity, with rupture of superficial cerebral veins or of "bridging" veins between the superomedial aspect of the cerebrum and the superior sagittal sinus. Because the superficial veins over the cerebrum are poorly developed in the preterm infant, this type of hemorrhage is seen less often in these infants. Bleeding over the posterior fossa involves bleeding below the tentorium and compression of the brainstem. Dural tears at the junction of the falx and tentorium near the attachment of the great vein of Galen are also associated with compression of the brainstem and midbrain (Inder et al., 2018a; Levene & de Vries, 2009; Neil & Inder, 2018).

Assessment. SDH must be distinguished from other types of intracranial hemorrhage and neurologic problems. This differentiation often can be accomplished by evaluating the infant's history and presentation and, if the infant is having seizure activity, by ruling out other causes of seizures. SDH over the cerebral hemispheres often is associated with SAH. SDH also occurs with extracranial hemorrhages, such as cephalohematoma and subgaleal, subconjunctival, and retinal hemorrhages; skull fractures; and brachial plexus or facial palsies. MRI or CT can assist in confirming the diagnosis; CT appears to be the imaging modality of choice (Inder et al., 2018a; Levene & de Vries, 2009; Neil & Inder, 2018).

Clinical signs of SDH relate to the site of the bleeding and the severity of the hemorrhage. Three patterns are seen in infants with bleeding over the cerebral hemispheres (Inder et al., 2018a). The first pattern is seen in most neonates with SDH; these infants have a minor hemorrhage and are asymptomatic or have signs such as irritability and hyperalertness. With the second pattern, primarily focal seizures develop during the first 2 to 3 days of life. Other neurologic signs that may be seen include hemiparesis; pupils that are unequal and respond sluggishly to light; full or tense fontanelle; bradycardia; and irregular respirations. The third pattern is seen in a few infants who have no or nonspecific signs in the neonatal period but in whom signs appear at 4 weeks to 6 months of age. These infants generally show increasing head size as a result of continued hematoma formation, poor feeding, failure to thrive, altered level of consciousness, and, occasionally, seizures caused by the chronic subdural effusion. Infants with abnormal neurologic signs from birth often have had bleeding over the posterior fossa with tentorial lacerations. Signs include stupor or coma, eye deviation, asymmetric pupil size, altered pupillary response to light, tachypnea, bradycardia, and opisthotonos. As the clot enlarges, these infants rapidly deteriorate, with signs of shock appearing over minutes to hours. The infant becomes comatose and has fixed, dilated pupils and altered respirations and heart rate, which culminate in respiratory arrest. Infants with small tears in the posterior fossa may have no clinical manifestations for the first 3 to 4 days of life. During this time, the clot gradually enlarges until signs of increased ICP appear. As the brainstem becomes compressed, the infant's condition deteriorates, and oculomotor abnormalities, altered respiration, bradycardia, and seizures occur (Inder et al., 2018a).

Management. Infants with a history of perinatal trauma or other risk factors are observed for seizures and other neurologic signs. Care is primarily supportive and includes maintenance of oxygenation and perfusion and provision of warmth, fluids, and nutrients. Nursing management also involves helping the parents to understand the basis for and the cause and prognosis of this type of hemorrhage, as well as the care of their infant.

Symptomatic infants with bleeding over the temporal convexity and increased ICP may require surgical evacuation if the infant's condition cannot be stabilized neurologically. Massive posterior fossa hemorrhage requires craniotomy and surgical aspiration of the clot (Inder et al., 2018a; Levene & de Vries, 2009). Infants at risk for SDH should be monitored carefully over the first 4 to 6 months after birth for late signs of bleeding and hematoma formation. Monitoring of these infants includes observation of head size, growth, feeding, activity, and level of consciousness, as well as monitoring for seizure activity.

Outcomes. The prognosis varies with the location and severity of the hemorrhage. Infants with bleeding over the cerebral hemispheres who are asymptomatic do well, as do most infants who have transient seizures in the neonatal period if no associated cerebral injury is present. Early diagnosis with CT or MRI has improved the outcome for infants with posterior fossa hemorrhage. Most infants with bleeding over the tentorium or falx cerebri die; severe hydrocephalus and neurologic sequelae usually develop in those who survive (Inder et al., 2018a).

Intracerebellar Hemorrhage. Intracerebellar hemorrhage is rare and is thought to be multifactorial with primary importance of birth trauma (breech or forceps delivery) and circulatory events. These hemorrhages occur in both term and preterm infants but are more common in preterm infants. Intracerebellar hemorrhage is seen during autopsy in infants with a history of perinatal hypoxic-ischemic events or severe respiratory distress syndrome (or both) and IVH (Bonifacio et al., 2011; Inder et al., 2018a).

Two presentations have been described. Many infants are critically ill from birth, with rapidly progressive apnea, a declining Hct value, and death within 24 to 36 hours. Other infants are less ill initially, and symptoms develop up to 2 to 3 weeks of age. Clinical manifestations include apnea, bradycardia, hoarse or high-pitched cry, eye deviations, opisthotonos, seizures, vomiting, hypotonia, and diminished or absent Moro reflex. Hydrocephalus often develops in these infants as early as the end of the first week after birth. The prognosis is poor in survivors, especially those born prematurely or with severe hemorrhage (Bonifacio et al., 2011; Inder et al., 2018a; Levene & de Vries, 2009).

Perinatal Stroke. Ischemic strokes are more common in the perinatal period than at any other time of life and are the leading cause of hemiplegic cerebral palsy, yet until recently have been poorly understood and oftentimes not diagnosed in the neonatal period. As a result, incidence is estimated to be from fairly rare (17–93 per 100,000 live births) to relatively common (1 in 1,600–5,000 live births; Benders, Groenendaal, & de Vries, 2009; Chabrier, Husson, Dinomais, Landrieu, & Nguyen, 2011; Cheong & Cowan, 2009; Inder & Volpe, 2018c; Kirton & deVeber, 2009; McAdams & Traudt, 2018; Mineyko & Kirton, 2011; Myers & Ment, 2012). Evidence suggests that preterm infants are just as likely, if not more likely, than term infants to experience perinatal ischemic stroke (Benders et al., 2009; Cheong & Cowan, 2009; Lynch, 2009; Myers & Ment, 2012). Stroke affects about 1 in 140 preterm births up to and including 34 weeks' gestation. Perinatal arterial ischemic strokes (AIS) account for 80% of diagnosed strokes in the neonatal period; the remaining 20% result from cerebral sinovenous thrombosis (CSVT; Inder & Volpe, 2018c).

Perinatal stroke was defined in 2006 by the National Institute of Child Health and Human Development and the National Institute of Neurological Disorders as the result of a focal disruption of cerebral blood flow secondary to an arterial or venous thrombosis or embolism occurring between 20 weeks' gestation and 28 postnatal day of life (Inder & Volpe, 2018c; Kirton & deVeber, 2009; McAdams & Traudt, 2018; Mineyko & Kirton, 2011; Myers & Ment, 2012). Perinatal strokes are further classified as fetal or neonatal. Fetal stroke is defined as having occurred between 20 weeks' gestation and the onset of labor or cesarean section and neonatal stroke as having occurred between the onset of labor and actual delivery. Presumed perinatal ischemic strokes are those identified by neuroimaging in infants greater than 28 days of life as having had a focal infarction at some point between 20 weeks' gestation and postnatal day 28 (Chabrier et al., 2011; Kirton & deVeber, 2009; Lynch, 2009; Myers & Ment, 2012).

Risk factors for perinatal stroke seem to be multifactorial and are still being identified to determine which factors are associated with a predilection for or direct causation of stroke. The risk factors that are being studied can be grouped into maternal, pregnancy/labor-related, and fetal or neonatal conditions (Inder & Volpe, 2018c; Lynch, 2009; McAdams & Traudt, 2018; Myers & Ment, 2012). Maternal risk factors include thrombophilias (factor V Leiden, factor VIII, protein S deficiency, protein C deficiency, prothrombin mutation, and antiphospholipid antibodies), preexisting conditions such as thyroid disease, diabetes mellitus, or gestational diabetes or history of infertility. Pregnancy/labor-related risk factors implicated in perinatal stroke include significant maternal trauma, primiparity, placental abnormalities, oligohydramnios, decreased fetal movement, prolonged rupture of membranes, chorioamnionitis, prolonged second stage of labor, or assisted delivery (vacuum or forceps). Fetal or neonatal risk factors include fetal distress during labor, cord abnormalities (tight nuchal or body cord, true cord knot), thrombophilias (same as maternal), congenital cardiac defects, and corrective surgery (Cheong & Cowan, 2009; Inder & Volpe, 2018c; Kirton & deVeber, 2009; Mineyko & Kirton, 2011; Myers & Ment, 2012). In addition, there may be a gender effect on incidence of stroke, with male gender being a risk factor over female gender (Chabrier et al., 2011; Cheong & Cowan, 2009; Kirton & deVeber, 2009; McAdams & Traudt, 2018; Myers & Ment, 2012).

Clinical signs and symptoms of perinatal stroke are determined by the timing of the initial insult. Seizures occur in 85% to 92% of affected newborns and are often the earliest manifestation of a perinatal stroke in an otherwise healthy appearing newborn. Most seizures happen within the first 72 hours of life; approximately 50% of seizures are focal motor, 33% generalized motor, and 17% subtle (Inder & Volpe, 2018c; Myers & Ment; 2012). Physical examination may reveal a bulging and/or pulsatile fontanelle, dilated head and neck veins, papilledema, asymmetrical movements or primitive reflexes, or seizure-like activity. Transient hemiparesis or generalized tone anomalies, such as hypotonia, are seen in the early newborn phase. Other symptoms of stroke are hypotonia and apnea, which are generic symptoms of any aberration in the newborn period, necessitating differential diagnosis from hypoxic, metabolic, and infectious disorders. Infants not diagnosed during the newborn stage are typically identified at a median of 6 months when asymmetry of reach and grasp is noted. Seizures occurring after 28 days of life and language delay have also been reported (Inder & Volpe, 2018c; Kirton & deVeber, 2009; McAdams & Traudt, 2018; Myers & Ment, 2012).

Diagnostic workup includes thorough history, newborn assessment, laboratory tests, and cardiac and neurologic imaging. Echocardiogram and electrocardiogram may be indicated to assess for cardiac dysfunction or rhythm disorders. EEG and neuroimaging are definitely indicated to evaluate for perinatal stroke (Inder & Volpe, 2018c; Kirton & deVeber, 2009; McAdams & Traudt, 2018; Mineyko & Kirton, 2011; Myers & Ment, 2012). During the past decade, rapid advances in the use of good quality early cranial ultrasonography and MRI with diffusion weighted sequences have facilitated improved and rapid diagnosis in the neonatal period, allowing for earlier identification and treatment and support of the affected newborn. Treatment of perinatal stroke is supportive and is directed at minimizing secondary brain injury and optimize outcome. Blood glucose, temperature, ventilation, oxygenation, and blood volume and pressure should be normalized. Hyperthermia and hyperthermic environment should be avoided. Seizures are documented and treated aggressively (Cheong & Cowan, 2009; Inder & Volpe, 2018c; Kirton & deVeber, 2009; McAdams & Traudt, 2018; Myers & Ment, 2012).

Outcome for infants with perinatal stroke varies with the area of the original insult. It is estimated that 20% to 70% of hemiplegic cerebral palsy cases are associated with perinatal stroke, with the spasticity more marked in the upper extremities. Intelligence is within normal parameters for two-thirds of affected infants (Myers & Ment, 2012).

Skull Fracture

Two types of skull fractures, linear and depressed, are uncommon but can be seen in newborns (Bonifacio et al., 2011; Hoppe & Benedetti, 2018; Volpe, 2018; White, Bouchard & Goldberg, 2018). Skull fractures occur in utero, during labor, with forceps delivery, or during a prolonged, difficult labor with compression and battering of the fetal skull against the maternal ischial spines, sacral promontory, or symphysis pubis (Bonifacio et al., 2011; Hoppe & Benedetti, 2018; White et al., 2018). The fetal skull often is able to tolerate mechanical stressors relatively well, because it is flexible, malleable, poorly ossified, and less mineralized than the adult skull. Depressed fractures occur after forceps delivery but occasionally are seen after a vaginal or cesarean birth. Compression of the skull causes buckling of the inner table without a break in the continuity of the skull. Linear fractures usually occur over the frontal or parietal bones. These fractures often are associated with extracranial hemorrhage and may underlie a cephalohematoma and are usually asymptomatic. Skull radiographs are required for the diagnosis (Hoppe & Benedetti, 2018; Tekes, Pinto, & Huisman, 2011; Volpe, 2018a; White et al., 2018). Intracranial hemorrhage rarely complicates linear fractures.

A depressed skull fracture is a visible, palpable depression, or dent in the skull, usually over the parietal area. These fractures often are described as resembling a ping-pong ball because the depression does not involve any loss of bone continuity. Unless underlying cerebral contusion or hemorrhage is present, no other signs or symptoms are seen (Bonifacio et al., 2011; Tekes et al., 2011). The diagnosis is confirmed with skull radiographs or CT scans. CT is performed to identify cerebral contusions or hemorrhage (Tekes et al., 2011; Volpe, 2018a; White et al., 2018).

Nursing assessment includes monitoring infants identified with skull fractures for signs of neurologic dysfunction, intracranial hemorrhage, meningitis, and seizures, although these findings are rare. Parents usually are concerned about their infant's appearance (with a depressed fracture) and the possibility of brain damage. They need support and teaching. Infants with uncomplicated linear fractures require no special management. Follow-up monitoring usually is recommended so that a growing fracture and development of a leptomeningeal cyst can be ruled out (Volpe, 2018a; White et al., 2018). Infants with basal fractures are treated for shock and hemorrhage.

In some infants with a depressed fracture, the fracture elevates spontaneously within the first week. Most clinicians recommend manually elevating an uncomplicated depressed fracture that does not elevate spontaneously within a few days (Tekes et al., 2011). After this time, manual elevation is more difficult or impossible. Surgical intervention usually is necessary if manual elevation fails, if the fracture is more severe and bone fragments are in the cerebrum, if neurologic deficits exist, or if ICP is increased.

Linear fractures heal spontaneously with no sequelae unless underlying cerebral damage or a growing fracture is present. Basal fractures are associated with high mortality and poor developmental outcome. Infants with depressed fractures that are small or treated early (or both) have a good prognosis. Infants with large fractures, especially if treatment is delayed, have a greater risk of sequelae. Unless a depressed fracture has lacerated the dura (a rare occurrence), neurologic deficits in these infants usually are caused by cerebral injury from the original trauma or a hypoxic event, or both, rather than by the fracture (Bonifacio et al., 2011; Hoppe & Benedetti, 2018; Volpe, 2018a). Infants with skull fractures should undergo regular evaluation of growth and development during infancy and early childhood.

Spinal Cord Injury

Spinal cord injuries are uncommon and usually occur in the midcervical to lower cervical and upper thoracic areas. Injury can occur at any point along the cord. Spinal cord injuries are caused by excessive traction, rotation, and torsion of the vertebral column and neck. Injury usually does not result from compression, but rather from stretching of the spinal cord, which is less flexible than the bony vertebral column. Damage to the spinal cord ranges from complete transection to laceration, edema, hemorrhage, and hematoma formation. Hemorrhage into the lining of the arteries may result in thrombosis, infarction, and ischemic cord damage. Risk factors are breech delivery (major factor), dystocia, macrosomia, and cephalopelvic disproportion (Bonifacio et al., 2012; Volpe, 2018a).

Infants with partial spinal cord injury have subtle neurologic signs and variable degrees of spasticity. Infants with high cervical or brainstem injuries are stillborn or die shortly after birth from respiratory depression, shock, and hypothermia. Infants with midcervical or upper cervical injury may be stillborn, born with marked respiratory depression, or have respiratory depression, with the neurologic injury going unrecognized until flaccidity, immobility of the legs, urine retention, or all three are noted. If born alive, these infants usually die within the first week, after development of progressive central respiratory depression that often is complicated by pneumonia. Other findings in this group of infants include relaxation of the abdominal wall, absent sensation in the lower half of the body, absent deep tendon and spontaneous reflexes, brachial plexus injury, and constipation. This group also includes infants with injuries at the C8 to T1 level who usually survive and may have a transient paraplegic paralysis at birth. Infants with mild injury may recover most or all of their function. Infants with moderate to severe damage are paraplegic or quadriplegic and have permanent neurologic damage (Bonifacio et al., 2011; Volpe, 2018a).

Initially, clinical manifestations are those of spinal cord shock, with hypotonia, weakness, flaccid extremities, sensory deficits, relaxed abdominal muscles, diaphragmatic breathing, Horner syndrome (ipsilateral ptosis, anhidrosis, and miosis), and a distended bladder. Infants with low cervical lesions have shallow, paradoxical respirations; these infants do not sweat. The skin over the affected area is dry and warm. Pinprick and deep tendon reflexes are absent. Areflexia may be noted over the upper and lower extremities in some infants. The degree of neurologic insult often cannot be accurately evaluated until the infant has recovered from the initial period of spinal shock and any edema or hemorrhage has been reabsorbed (Madsen, Frim, & Hansen, 2005; Volpe, 2018a). After several weeks or months, a paraplegic autonomic hyperreflexia develops that is characterized by periodic mass reflex response. This results in tonic spasms of extremities, spontaneous micturition, and profuse sweating over the paralyzed area (Volpe, 2018a).

Initial management focuses on stabilization, treatment of associated problems (e.g., asphyxia, hemorrhage, shock), and management of respiratory depression. Infants with midcervical to upper cervical or brainstem lesions require assisted ventilation. Parents are in shock initially and need time to grieve. They need continuing support and teaching regarding the care of the infant. Ongoing management of these infants and their families requires a multidisciplinary team that includes the disciplines of nursing, medicine, neurology,

neurosurgery, physical therapy, orthopedics, urology, social work, and psychology. Ultrasonography, CT, or MRI may be performed to determine the level and the extent of injury (Volpe, 2018a).

Skin integrity over the paralyzed area must be maintained to prevent pressure areas and skin breakdown. Thermoregulation may be a problem, because evaporative loss through the skin is reduced over the affected body parts in the initial period of the recovery process. The infant is positioned and repositioned regularly to promote normal alignment of body parts and prevent development of contractures and decubiti. The affected areas should be kept clean and dry and massaged with gentle, passive range-of-motion exercises. These infants need meticulous bowel and bladder care to prevent urinary tract infection and skin excoriation. Glycerin suppositories at regular intervals can help normalize bowel function. Infants are also monitored for signs of respiratory infection and pneumonia. Parental teaching before discharge focuses on normal baby care issues and concerns, as well as the special needs of a paralyzed infant.

The prognosis depends on the level and severity of the injury, but it generally is poor. Many infants with spinal cord injury are stillborn or die shortly after birth, particularly those with midcervical to high cervical or brainstem injuries. Those who survive have varying degrees of residual paralysis, respiratory problems, and bowel and bladder dysfunction, depending on the level of the injury. Most surviving infants have a spastic quadriplegia. Infants with involvement of the intercostal muscles and diaphragm often are ventilator dependent (Bonifacio et al., 2011; Volpe, 2018a).

Peripheral Nerve Injuries

Peripheral nerve injuries result from stretching, compression, twisting, hyperextension, or separation of nerve tissue (Bonifacio et al., 2012; Levene & de Vries, 2009; Volpe, 2018a). Injury can occur before, during, or after birth. Damage can range from swelling of the nerve to complete peripheral degeneration (with later total recovery) to complete division of all structures. The more common sites affected are the brachial plexus and the facial, phrenic, radial, median, and sciatic nerves. This type of injury is seen predominantly in term or LGA infants (Bonifacio et al., 2012; Volpe, 2018a).

Injury to the radial nerve usually results from compression of the nerve caused by fracture of the humerus during a breech delivery or by intrauterine compression of the arm. The infant has wrist drop with a normal grasp reflex. Recovery usually occurs over the first few weeks to months. Median and sciatic nerve injuries are typically postnatal iatrogenic events. Median nerve injury can be a complication of brachial or radial arterial punctures. These infants have diminished pincer grasp and thumb strength and a flexed fourth finger. Recovery is variable. Sciatic nerve injuries are often permanent. They arise from trauma from a misplaced intramuscular injection or from ischemia from an injection of hypertonic solutions into the gluteal muscle. Infants with this type of injury have diminished abduction and distal joint movement. Hip adduction, rotation, and flexion are unaffected (Levene & de Vries, 2009; Volpe, 2018a).

Facial Nerve Palsy. Facial nerve palsy has an incidence of 0.23% (Levene & de Vries, 2009). Injury to the peripheral nerve is caused by trauma from oblique application of forceps, prolonged pressure on the nerve during labor from the maternal sacral promontory, or pressure from an abnormal fetal posture. Although some investigators have not found any differences in incidence between forceps and spontaneous vaginal deliveries, others have noted a correlation between the type of forceps and the incidence of injury. The facial nerve of the newborn is superficial after it emerges from the stylomastoid foramen. As a result, the nerve is vulnerable to compression injury at this site or as it traverses the ramus of the mandible. The temporofacial and cervicofacial nerve branches are most often involved. The injury is most common on the left. Because the prognosis is favorable, the injury appears to be caused by hemorrhage or edema into the nerve sheath rather than by disruption of the nerve fibers (Levene & de Vries, 2009; Volpe, 2018a).

Facial nerve paralysis must be distinguished from asymmetric crying facies and nuclear agenesis. Asymmetric crying facies results from absence of the depressor muscle of the angle of the mouth. These infants close their eyes normally when crying, but the mouth does not move down and out. They suck without dribbling. This disorder generally is benign. Nuclear agenesis (Möbius syndrome) is a more significant disorder characterized by congenital paralysis of the facial muscles (Levene & de Vries, 2009; Terzis & Anesti, 2011; Volpe, 2018a).

Clinical manifestations vary, depending on whether the injury is to the central nerve, the peripheral nerve, or the peripheral nerve branch. The complete peripheral nerve injury results in a unilateral inability to close the eye or open the mouth. The lower lip on the affected side does not depress during crying, nor does the forehead wrinkle. The affected side appears full and smooth, with obliteration of the nasolabial fold. These infants dribble milk while feeding. The infant may be unable to close the eye on the affected side. Central injury usually results in a spastic paralysis of the lower portion of the face contralateral to the side of CNS injury without involvement of the eyes or forehead. Peripheral nerve branch injury results in varying degrees of paralysis of the forehead, eye, or lower face, depending on the branch involved. The paralysis is apparent at birth or within 1 to 2 days after birth.

Almost all infants recover completely. Improvement usually is apparent by 1 to 4 weeks, and complete recovery occurs after several months in most infants. Infants with severe nerve regeneration have a longer recovery period and may occasionally require later cosmetic surgery (Levene & de Vries, 2009; Terzis & Anesti, 2011).

Nursing management involves parent counseling and teaching and prevention of complications. The eye on the affected side is patched, and 1% methylcellulose eye drops are instilled every 3 to 4 hours to prevent corneal damage. Dribbling with sucking can be a transient problem. A neurosurgical consultation is recommended if no improvement is noted by 7 to 10 days or if further loss of function occurs. With partial degeneration, physical therapy, massage, or electrical stimulation may be used, although the efficacy of these therapies is controversial and not well documented. Electromyography, nerve excitability, or nerve conduction latency examinations may be performed to evaluate the extent of the damage (Terzis & Anesti, 2011).

Brachial Plexus Injury. Brachial plexus palsy involves injury of the C5 to T1 nerve roots and is seen almost exclusively in term infants. The incidence ranges from 0.5% to 2% (Volpe, 2018a). Injury to the brachial plexus results from excessive lateral flexion, rotation, or traction on the neck. The degree of injury varies, ranging from edema and hemorrhage of the nerve sheath to avulsion of the nerve root from the spinal cord. With mild-to-moderate injury the axons are shattered, but the nerve sheaths remain intact. This degree of intactness of the nerve sheaths promotes regeneration of the nerve by 3 to 4 months, with full recovery by 3 to 15 months in most infants (Alfonso, 2011; Doumouchtsis & Arulkumaran, 2009; Levene & de Vries, 2009; Volpe, 2018a). Severe injuries result in radicular rupture or intraspinal tearing of the nerve and division of the nerve into radicles. If radicular rupture occurs, the root loses contact with the spinal cord. These injuries do not recover spontaneously (Alfonso, 2011; Doumouchtsis & Arulkumaran, 2009; Levene & de Vries, 2009).

Brachial plexus injuries usually are unilateral and on the left side. Fracture of the clavicle may occur in conjunction with this type of injury. Brachial plexus injury can be seen in uncomplicated deliveries and after cesarean birth; however, this injury is usually associated with vaginal delivery of LGA infants, shoulder dystocia, breech

presentations, and prolonged labor or difficult delivery. Spontaneous injuries may occur from compression of the shoulder as it passes over the sacral prominence (Alfonso, 2011; Doumouchtsis & Arulkumaran, 2009; Levene & de Vries, 2009; Volpe, 2018a).

Clinical manifestations vary with the location and severity of the injury. Signs of injury usually are apparent from birth but may be delayed for several days to a few weeks in some infants. The major types of injury are Erb (Erb–Duchenne) palsy, an injury of the upper plexus involving C5 to C7, and Klumpke palsy or lower plexus injury at C5 to T1 (Levene & de Vries, 2009; Volpe, 2018a). With Erb palsy, the shoulder and upper arm are involved, and denervation of the deltoid, supraspinous, biceps, and brachioradialis muscles occurs. The arm lies passively at the infant's side, abducted and internally rotated, and the forearm is pronated. The wrist and fingers are flexed. This posture is referred to as the "waiter's tip" position. The Moro reflex is absent, and the biceps and radial reflexes are diminished or absent on the affected side; the grasp reflex is normal.

Klumpke palsy is seen primarily in breech infants whose arm has been hyperabducted and delivered with the head affecting the flexors of the wrist and hand. Cervical sympathetic fibers may also be affected; sweating and sensation are absent in the affected hand and arm. The infant holds the affected arm at the side of the thorax with the hand in a claw hand posture. The Moro and grasp reflexes are absent, and the triceps reflex is diminished or absent on the affected side; biceps and radial reflexes are present. If the T1 root is affected, the infant manifests Horner syndrome (Bonifacio et al., 2012; Levene & de Vries, 2009; Volpe, 2018a).

Erb–Klumpke (total) palsy is characterized by entire arm and hand involvement as a result of injury to the nerve roots of the brachial plexus from C5 to T1. Complete paralysis of the upper and lower arm and hand, flaccidity, and accompanying sensory, trophic, and circulatory changes are noted. Deep tendon and Moro reflexes are absent. If the C4 roots are also affected, an associated phrenic nerve (diaphragmatic) paralysis occurs. Involvement of the T1 root leads to Horner syndrome in about one-third of these infants (Levene & de Vries, 2009; Volpe, 2018a).

Initial management focuses on protecting the arm until localized edema and pain subside. MRI or CT is used to visualize the degree of injury. The affected arm should not be splinted or immobilized, as it has not proven beneficial to prevent contractures and further stretching of the plexus as had previously been thought. After edema subsides, at about 7 to 10 days, physical therapy gradually is instituted as the infant can tolerate it. Gentle passive range-of-motion exercises have been shown to minimize formation of contractures and to reduce permanent disability. These infants have continued physical therapy consisting of massage and exercise over the first months until total or partial recovery occurs (Volpe, 2018a). Infants with a brachial plexus injury should be evaluated for associated problems, including fractures and respiratory difficulty secondary to phrenic nerve paralysis. If improvement is not noted within the first few months, electromyography and nerve conduction studies are performed to determine the extent of the damage, to follow recovery, and to determine whether surgical intervention is needed (Volpe, 2018a). Infants with brachial plexus injuries often experience considerable pain during movement of the affected arm in the first few weeks after birth. Nursing management is directed at reducing passive and active movement of the arm and providing comfort measures to reduce pain. The paralyzed arm is supported in a position of relaxation. Parent teaching regarding positioning, prevention of contractures, and exercise is essential.

The prognosis depends on the level and severity of the injury. Approximately 65% to 95% of infants have full recovery with supportive care. Many infants recover by 3 to 4 months of age and more than 90% by 2 to 3 years. Erb palsy, the most common type of injury, has the best prognosis for full recovery. Infants with total paralysis are most likely to have residual paralysis. Residual functional deficits include alteration in abduction and external rotation of the shoulder; restricted movement of the elbow, forearm, and hand; and hand weakness. These functional impairments can lead to abnormal muscle development and arm growth (Levene & de Vries, 2009; Volpe, 2018a).

Phrenic Nerve Palsy. Phrenic nerve palsy is caused by injury of the cervical nerve roots at C3 to C5. The injury results from tearing of the nerve sheath, which is accompanied by edema and hemorrhage. Phrenic nerve palsy may occur as an isolated event or in association with brachial nerve palsy. Risk factors, especially breech delivery, are similar to those for brachial plexus injury. Paralysis of the diaphragm is a result of damage to the phrenic nerve. The injury usually is unilateral and on the right side. Because the diaphragm is paralyzed, infants with phrenic nerve injury have respiratory difficulty. This phenomenon must be differentiated from CNS, cardiac, and pulmonary problems (Gauda & Martin, 2018; Levene & de Vries, 2009; Volpe, 2018a).

Infants with mild-to-moderate phrenic nerve injury may have early respiratory difficulty, suggestive of hypoventilation that stabilizes or improves. The infant may have recurrent episodes of cyanosis and dyspnea. Respiratory efforts result in primarily thoracic movement with minimal or no abdominal excursions, opposite of the normal newborn breathing pattern. Infants with complete avulsion or bilateral injury have severe respiratory distress from birth, with tachypnea, apnea, and a weak cry (Gauda & Martin, 2018; Volpe, 2018a).

Management focuses on promoting ventilation and oxygenation. Infants are not enterally fed initially until respiratory status improves. Infants with severe distress require positive pressure ventilation or constant positive airway pressure for support until recovery occurs. Surgical plication of the diaphragm is performed if no improvement is noted or if the infant is still ventilator dependent at 4 to 6 weeks of age (Gauda & Martin, 2018; Volpe, 2018a).

The infant is positioned on the affected side. If the infant cannot be fed, adequate fluid and calories must be provided. Feeding is instituted gradually, most likely by gavage tube initially. When oral feeding is started, the infant is fed slowly and given ample opportunity for rest and monitoring of respiratory status. Because recovery takes several months, parents must be taught feeding, positioning, and comfort techniques. The developmental needs of infants requiring prolonged hospitalization must be met; sensory input and play activities appropriate to their maturity and health status must be provided. Most infants recover by 6 to 12 months of age. Other infants recover clinically but have residual abnormalities of diaphragmatic movement on radiography (Gauda & Martin, 2018; Volpe, 2018a).

SUMMARY

Infants with neurologic dysfunction present a significant challenge to the neonatal nurse. The nurse must respond to infants with life-threatening conditions, such as perinatal hypoxic-ischemic injury and intracranial hemorrhage; to those with transient problems, such as an isolated seizure; and to those with chronic problems, such as NTDs. Nurses must also deal with their own responses and those of the families of infants who may die during the neonatal or early infancy periods or whose short-term and long-term outcome may be altered by the extent of neurologic insult. To optimally care for these infants and their families, nurses must understand the basis for, and the implications of, specific types of neurologic dysfunction; they must recognize the clinical manifestations of these types of dysfunction; and they must respond appropriately in concert with other healthcare professionals.

The nursing care of infants who have or who are at risk for neurologic dysfunction involves assessment and monitoring of the infant's neurologic status and responses to the extrauterine environment, as well as of subtle signs that may indicate a change in status. Nursing management of the infant involves activities to address alteration in level of consciousness, potential for injury related to trauma or infection, impairment of skin integrity, alterations in comfort, impaired mobility, alterations in thermoregulation, alterations in nutrition and fluid and electrolyte status, and promotion of neurobehavioral organization and development. The nurse must also assess family coping, interactive processes, knowledge, and grieving to assist the family in coping with the birth of an ill infant and, for many families, with the uncertainty or certainty of long-term neurologic deficits in their infant.

CASE STUDY

■ **Identification of the Problem.** Term female infant vaginal delivery with vacuum assist; presented with apnea, no tone, requiring resuscitation intervention.

■ **Assessment: History and Physical Examination.** The term female infant was delivered vaginally to a 24-year-old G2 P1 woman following prolonged labor at term after an uncomplicated pregnancy. The vaginal delivery was assisted with a vacuum apparatus. Gestational age was term with a birth weight of 3.3 kg.

Upon delivery, the infant was limp, cyanotic/pale, and apneic. The infant was successfully resuscitated following the Neonatal Resuscitation Program (NRP) guidelines; required 2 minutes positive pressure ventilation by T-piece resuscitator to initiate effective ventilation when spontaneous respirations were noted; infant received 10 minutes of CPAP via the T-piece resuscitator; heart rate was greater than 100 beats/minute (bpm) by 1 minute of age. Pulse oximetry was initiated by 1 minute of age, reading 44% oxygen saturations initially and gradually improved to 85% by 5 minutes of life; room air was used throughout resuscitation.

She remained pale with thready pulses and poor peripheral perfusion at 10 minutes of life; spontaneous respiratory rate 40 to 60 seconds with easy respiratory effort without CPAP; pulse oximetry saturations 88% to 94%; heart rate 160 seconds. The infant was brought to the NICU for ongoing care.

Apgar scores were 4^{1}, 6^{5}, 8^{10}

■ Physical Examination on Admission to the NICU

GENERAL: pale with thready pulses, poor peripheral perfusion; heart rate 180 bpm. Respiratory rate 46, shallow; saturations 88% to 92% in room air

HEENT: increasingly boggy, enlarging scalp hematoma; eyes open, no blink; pupils reactive to light; positive red reflex and normal facies

RESP: lung fields bilaterally clear and equal to bases; gasping respiratory effort

CV: rate regular with no murmur noted. Poor peripheral perfusion, capillary blood refill time greater than 5 seconds, and thready pulses were noted

ABD: abdomen soft and nontender with no hepatosplenomegaly or masses palpable; three-vessel cord. The anus appeared patent

Genitourinary: normal female infant genitalia

NEURO: decreased responses, with eyes open and unblinking; extremities were well formed; muscle tone was markedly decreased

SKIN: pale with general cyanotic undertones, pronounced circumoral and acrocyanosis

EXTREMITIES: well formed; 10 digits per extremity; generalized cool and mottled. Umbilical arterial and venous catheters were placed, and 10 mL/kg normal saline was given for volume expansion; dopamine was initiated because of low blood pressure and ongoing poor perfusion. Labs were drawn via the umbilical arterial catheter: arterial blood gas, complete blood count (CBC)/differential, and disseminated intravascular coagulation (DIC) panel, transfusion panel (type and cross for transfusion). The scalp hematoma was noted to be rapidly enlarging during this time. The infant was immediately intubated and was given an emergency blood transfusion of 15 mL/kg.

■ Differential Diagnoses

- Subgaleal hemorrhage
- Perinatal hypoxic-ischemic injury
- Shock
- DIC
- Intracranial hemorrhage
- Sepsis screen
- Congenital cardiac defects screen

■ Diagnostic Tests

Laboratory Tests:

- CBC/differential: WBC 10.3, segmented cells 44; bands 1; Hct 21%, platelet count 168,000/mm^3
- Coagulation (DIC) panel: prothrombin time (PT) greater than 100 seconds, partial thromboplastin time (PTT) greater than 100 seconds, fibrinogen 54 mg/dL, and D-dimers 2 to 4 mg/mL
- Blood, tracheal, and surface cultures for bacterial and/or viral infections: all negative

Imaging Tests:

- Head CT scan (performed within 4 hours of age): extensive blood within the extracranial soft tissues, mild IVH and SAH
- Transcranial Doppler and nuclear medicine flow scan (performed at 24 hours of age): no cerebral blood flow
- EEG (performed on day of life 3): absence of cortical activity

■ Working Diagnosis

Extensive subgaleal hemorrhage with hematoma

Based on clinical, laboratory, and imaging findings, data from history and physical assessment

■ Development of Management Plan

Continuous monitoring of arterial blood pressure, vital signs, and neurologic status, every 2 to 4 hours Hct, platelet count, PT/PTT, and fibrinogen

Maintenance fluid support; fluid boluses to support intravascular volume

Ensure adequate blood volume, clotting factors: colloids (fresh frozen plasma with cryoprecipitate, whole blood, packed red blood cells, platelets) as needed to treat DIC, anemia

Respiratory support with mechanical ventilation as needed

Vasopressors to maintain adequate blood pressure and cerebral blood flow

Antibiotics until cultures negative for 72 hours

■ Implementation and Evaluation of Effectiveness

Implementation of management plan: (immediately after initial assessment in the NICU)

The infant was intubated within the first half hour of life

Multiple blood transfusions, fresh frozen plasma with cryoprecipitate, whole blood and packed red blood cell transfusions, and normal saline boluses given to normalize the coagulation studies by 24 hours of age, with a total of 476 mL neonatal red blood cells, 8 U of cryoprecipitate, and 140 mL of fresh frozen plasma

Dopamine 10 mcg/kg/minute initiated by 1 hour of life; weaned to 5 mcg/kg/minute by 36 hours

■ Effectiveness of Management Plan

Respiratory status stable by 2 hours of life

Blood pressures were normalized by 2 hours of life

Metabolic acidosis and coagulation panel results were normalized within the first 24 hours of life

Severe brain involvement was suspected on day of life 2, with dismal results of the Doppler and flow scan and flat EEG results

■ **Outcome.** Brain death was determined on day of life 3. Life support was terminated on day of life 4. The autopsy was remarkable for an extensive subgaleal hematoma and moderate SAH and SDH.

CASE STUDY

■ **Identification of the Problem.** A 6-day-old former term infant turned blue at home on day of life 4 and was admitted to the local hospital.

■ **Assessment: History and Physical Examination.** A 6-day-old former term neonate was delivered vaginally following an uncomplicated pregnancy with a birth weight of 2,990 g. Prenatal laboratory results were remarkable for positive group B streptococcus (GBS) vaginal culture, for which the mother received prophylactic perinatal antibiotics. The infant did well after delivery, breastfed vigorously, and was discharged home with his mother on day 2 of life. At the time of admission, his weight was 2,950 g, occipitofrontal circumference was 33 cm, and length was 49.5 cm.

After initial admission to the local hospital, the infant was screened for sepsis (normal CBC and differential, negative cultures for viral and bacterial sepsis). On day 2, at the local hospital, the infant had a seizure consisting of lip smacking, apnea, cyanosis, and bicycling of lower extremities; was given 10 mg/kg phenobarbital; and was taken to CT, which showed a right IVH. The infant was transferred to the NICU of the tertiary care hospital.

■ Physical Examination

GENERAL: vital signs within normal limits; somewhat sleepy and irritable with handling

HEENT: anterior fontanelle large and soft, with sutures split to just above eyebrows, lateral sutures proximate. Pupils equal and reactive to light; bilateral positive red reflex; sunset eyes when crying; nares patent bilaterally; palate and clavicles intact

LUNGS: clear and bilaterally equal; easy work of breathing with spontaneous respirations

CV: heart regular rhythm and rate, no murmur; peripheral pulses 2+ in all extremities, good peripheral perfusion; capillary blood refill time ~3 seconds

ABD: abdomen was soft and nontender; liver right costal margin; no hepatosplenomegaly or masses palpable; umbilical stump dry

GU: normal male genitalia; testes bilaterally descended; well-developed scrotum

NEURO: arched with handling, moved all extremities with increased tone; occasional tongue thrust; positive sunset eyes, positive gag reflex, positive blink response; no clonus

EXTREMITIES: well formed with good muscle mass, 10 digits/extremity

SKIN: pale pink; good turgor and healing areas from previous lab draws and intravenous access attempts. No petechiae or rashes were noted

SOCIAL: maternal history is significant, for a cousin died of "fits" at 3 months of age; other relatives suffered frequent bone fractures or sundown eye sign; father is reportedly short-statured with short-statured children

■ Differential Diagnoses

- Seizures of unknown etiology
- Rule out herpes simplex infection and other viral or bacterial meningitis
- Rule out brain structure abnormalities
- Rule out nonaccidental trauma (NAT)
- Rule out intracranial and intraventricular hemorrhage
- Hypoventilation of unknown etiology

■ Diagnostic Tests

Laboratory Tests:

- CBC/differential: WBC 10.6, segmented cells 27, bands 0, Hct 60.2%, platelet count 254,000/mm^3
- Electrolytes: sodium 132, potassium 4.7, chloride 96, bicarbonate 29, calcium 11.9, ionized calcium 1.42, phosphorus 2.9, alkaline phosphorus less than 5, ammonia 45, lactate 2.2, BUN less than 1, and serum glutamic-oxaloacetic transaminase 33
- Blood and central spinal fluid bacterial and viral cultures: negative
- Urine drug screen: negative

Imaging Tests:

- Serial EEGs: excessive background discontinuity and prominent high-amplitude spikes and polyspikes, but no seizures; repeat EEG (hospital day 7) significantly improved but still mildly abnormal due to focal moderate amplitude, midline vertex, and negative spikes without seizure activity
- MRI of the brain: hemorrhage located either in subependymal location or cavum velum interpositum not consistent with shear injury
- Head CT: placement of the hemorrhage in the right thalamic area with extension into the lateral ventricles and stable ventricle size

Consults: (pediatric specialists)

- NAT team: ophthalmic examination: normal without ocular hemorrhages; skeletal radiographic study no fractures; evidence of metaphyseal fraying in the lower extremities consistent with developing rickets

Neurology, metabolic, and endocrine services

■ Working Diagnosis

Six-day-old infant with seizures due to probable hypophosphatemia

Laboratory results effectively ruled out sepsis, meningitis, electrolyte imbalances, and metabolic disease as etiologies for seizure activity

The extremely low-alkaline phosphorus, low phosphorus, and high calcium and ionized calcium levels were indicators for endocrine disease

EEG was moderately abnormal due to excessive background discontinuity and prominent high-amplitude spikes and polyspikes, but no seizures and improved by hospital day 7

Imaging results ruled out NAT and other structural causes for the clinical presentation of seizure-like activity

Skeletal radiographic study gave further support for endocrine disease due to the early radiographic indication for rickets

NAT team concluded that the seizures were not caused by brain injury due to NAT

Neurology service concluded that the etiology of the seizures was not structural or related to brain injury but most likely due to pyridoxine deficiency or some endocrine or metabolic syndrome

Endocrinologists considered the seizures to be related to hypophosphatasia

■ Development of Management Plan

Monitor the infant

Provide respiratory, fluid, and nutritional support with a low-calcium formula

Initiate vitamin D supplements to delay bone decalcification and rickets

Provide teaching and support for the parents

Arrange follow-up with the primary care provider and the pediatric neurology, orthopedic, and endocrinology services

■ Implementation and Evaluation of Effectiveness. During the examination phase, pyridoxine was given for a seizure-like event on hospital day 2 that included bicycling, sneezing, and clonic–tonic movements with paroxysmal respiratory pattern. Maintenance pyridoxine was given until hospital day 10, when it was determined the seizures were caused by hypophosphatemia. The infant was NPO with peripheral intravenous fluids until a special low-calcium formula could be delivered, and vitamin D supplements were started to delay bone decalcification and rickets. At the time of discharge, the infant was taking good amounts of the formula by nipple and gaining weight slowly. His mother was learning what little there is to know about this rare congenital disease and learning to prevent fractures as much as possible. Follow-up care was arranged with the primary pediatrician, neurology, orthopedics, and endocrinology.

■ Outcome. The prognosis for symptomatic congenital hypophosphatasia is poor, with death usually occurring within the first year of life. Parents initially denied being told about the infant's condition at first follow-up visit with the primary pediatrician; however, the parent was feeding the infant the correct formula and following all discharge instructions.

CASE STUDY

■ Identification of the Problem. A term infant male was limp and not breathing after home-birth delivery.

■ Assessment: History and Physical Examination. The infant boy was born at 40 6/7 weeks by vaginal delivery to a 24-year-old, G1 P0 > 1 woman at home with a certified nurse midwife present. Prenatal laboratory results and history were unremarkable with negative GBS status. The pregnancy was uncomplicated. Membranes were spontaneously ruptured with clear fluid approximately 11 hours prior to delivery, and no maternal fever was documented; the mother received antibiotics about 4 hours prior to delivery. Active pushing in second stage was 4 hours, followed by shoulder dystocia after the infant's head was delivered. The infant was limp and apneic after delivery. The certified nurse midwife performed mask-delivered positive pressure ventilation with room air with improvement in respiratory effort. Apgar scores were 1^{1}, 2^{5}, 4^{10}, 5^{15} per the nurse midwife report.

The infant was emergently brought to the NICU.

Admission weight: 3,765 g, head circumference: 37 cm, and length: 54 cm.

HEENT: anterior fontanelle was soft, flat, sutures opposed, proximate with a right cephalohematoma; eyes equal and reactive to light with a positive red reflex; nares bilaterally patent; palate and clavicles intact

RESP: breath sounds coarse bilaterally, slightly decreased over the lower right lung field. Increased work of breathing with increased subcostal and substernal retractions, slight tracheal tug, and flared nares

CV: mildly tachycardic, no murmur; peripheral pulses 1+ in all extremities; poor peripheral perfusion and capillary blood refill time of greater than 4 seconds. Low-borderline cuff blood pressure

ABD: abdomen soft and nontender; no hepatosplenomegaly or masses palpable; three-vessel cord

NEURO: responsive and alert on admission

EXTREMITIES: well formed; slightly decreased muscle tone

SKIN: pale pink and slightly mottled, with acrocyanosis and circumoral cyanosis

■ Development of Management Plan

- Nasal CPAP to support respiratory effort
- Peripheral intravenous fluids at 80 mL/kg/day maintenance
- Fluid bolus 10 mg/kg normal saline as needed
- Place umbilical arterial and venous catheters
- Chest radiograph confirmed right pneumothorax
- Needle aspiration was performed for small amount of air
- Chest radiographs as needed
- Monitor for abnormal activity showed pneumothorax resolved. Infant initially improved but on day 2 of life developed apnea, tonguing, lip smacking, and rhythmic extremity movement.

■ Differential Diagnoses

The differential diagnoses for an infant following a difficult delivery with positive pressure ventilation include:

- Respiratory distress versus transient tachypnea of the newborn
- Rule out pneumothorax
- Rule out hypoxic-ischemic encephalopathy
- Rule out intracranial hemorrhage
- Sepsis screen
- Shock
- Rule out seizures

- Congenital cardiac defects
- Metabolic and/or endocrine defects

■ Diagnostic Tests

Laboratory Tests:

- CBC with differential: WBC 11.7, segmented cells 33, bands 2; Hct: 56; platelets: 156,000/mm^3
- Blood cultures for bacterial and viral growth: negative
- Electrolytes, lactic acid, and ammonia levels, amino acid assays and urine organic acids, and liver function tests: normal

Imaging Tests:

- Chest radiography: small right pneumothorax
- Head CT: (24 hours of life) no evidence of hydrocephalus, ischemia, or intracranial hemorrhage
- Serial EEGs: (48 hours of life) moderate to severely abnormal EEG due to discontinuous low-amplitude background with asynchrony and frequent, subclinical, electrographic seizures from midline vertex and left central region. Second EEG: (72 hours) improvement from initial EEG with no electrographic seizures. There were positive sharp transient waves that were of concern for underlying structural abnormalities and can be consistent with anoxic and hypoxic events as reflected with clinical presentation. Third EEG: (5 days) abnormal due to predominantly right temporal sharp waves and possibly two brief electrographic seizures.
- MRI: (11 days) abnormalities on T2 and diffusion weighted imaging (DWI) consistent with perinatal HIE

Consult:

- Pediatric neurology: seizures due to HIE

■ Working Diagnoses

- Seizures due to HIE
- Respiratory distress
- Pneumothorax

■ Development of Management Plan

The management plan included:

- Monitoring
- Respiratory support with mechanical ventilation as needed
- Fluid support; initiate feeds
- Sepsis screen
- Antibiotics
- Needle aspiration of small right pneumothorax
- Chest tube insertion if indicated
- Lactic acid and ammonia levels, amino acid assays, and urine organic acids
- Expedite state newborn screen testing

■ Implementation and Evaluation of Effectiveness

Implementation of management plan: (immediately after initial assessment in the NICU)

- Antibiotics were given for 48 hours for the sepsis screen
- Right pneumothorax was reduced with needle aspiration and resolved without further intervention
- Seizure activity noted on day of life 2, confirmed with EEG, given phenobarbital 15 mg/kg, with resolution of the seizure
- Subsequently intubated at approximately 36 hours of life for a prolonged apnea event requiring positive pressure ventilation, given another 15 mg/kg phenobarbital loading dose and initial lorazepam (Ativan) dose to control seizures
- Metabolic etiology was ruled out with normal lactic acid and ammonia levels and normal amino acid assays and urine organic acids results
- State metabolic screening results were normal
- Neurologic examination deteriorated over the first 4 days, with the infant presenting with no gag, no corneal reflex, passive hypertonicity, active hypotonia, consistent and rhythmic hyperventilation, and periodic apnea, clonic–tonic movements of predominantly the left extremities by the end of day 3 of life, and persisting through day 5 of life
- Maintenance phenobarbital was initiated on day 3 of life, and lorazepam was given periodically for seizure activity during days 4 to 5 of life. Seizures were no longer observed after day 5 of life; infant gradually improved clinically with improved passive and active tone, improved gag and positive corneal reflex
- Extubated on day 6 of life to high-flow nasal cannula of 2 L/minute flow of room air; weaned quickly to room air without nasal cannula flow
- Feeds of expressed mother's milk had been initiated per gavage tube on day 3 of life; infant was tolerating full volume by day 7 by gavage every 3 hours. Breastfeeding and nipple feeds were initiated on day 8, but infant needed most of his feeds by gavage at time of discharge on day 18. Follow-up care was arranged for neurology clinic and EEG 1 month after discharge.

■ **Outcome.** Infant was discharged with phenobarbital and gavage feeds; was breastfeeding well, gaining weight, and thriving at the neurology follow-up appointment at 1 month of life.

EVIDENCE-BASED PRACTICE BOX

HIE is the major cause of encephalopathy in newborns. HIE is an injury to the brain caused by oxygen deficit resulting from either systemic hypoxemia or ischemia or a combination of the two conditions. The hypoxemia and ischemia may occur simultaneously or sequentially, and it appears from recent evidence that ischemia is the more important of the two oxygen deprivation states in causing the brain injury. Subsequent reperfusion of the affected brain area has been shown to be the time at which the majority of the injury to the brain occurs. Glucose deprivation also plays a part in the severity of the brain injury.

(*continued*)

EVIDENCE-BASED PRACTICE BOX (*continued*)

HIE causes transient organ dysfunction in 4 to 6 in 1,000 live births and results in death or significant neurologic deficits in 1 per 1,000 live births. Traditionally, the newborns affected by HIE have been treated by symptoms of the resultant multiorgan and multisystem effects. A recent development in proactive treatment with the use of controlled hypothermia has proven to be effective for newborns with moderate-to-severe HIE (Back & Volpe, 2018).

Induced mild hypothermia is increasingly the treatment of choice for infants greater than or equal to 36 weeks' gestation with moderate-to-severe HIE in addition to establishing ventilation and adequate perfusion and preventing or minimizing hypotension, hypoxia, and acidosis, rapid alterations in cerebral blood flow and systemic blood pressure, and severe apneic and bradycardic episodes in providing supportive care. Mild hypothermia is induced using either selective head cooling or whole-body cooling. A systematic review and meta-analysis of seven randomized controlled trials including 1,214 newborns done by Tagin, Woolcott, Vincer, Whyte, and Stinson (2012), provided evidence that hypothermia with either total body cooling or selective head cooling improves survival and protects neurodevelopment in newborns with moderate-to-severe HIE. Simbruner, Mittal, Rohlmann, Muche, and neo.nEURO.network Trial Participants (2010) reported that in their randomized controlled trial involving 129 newborns, of which 111 participated in neurodevelopmental follow-up at 18 months, hypothermia treatment provided strong neuroprotective effect for infants with severe HIE. A multicenter international randomized controlled trial done by Jacobs et al. (2011) provides supporting evidence that whole-body hypothermia reduced the risk of death or major disability at 2 years of age.

Selective hypothermia, if begun within 6 hours of life and carefully controlled within a tertiary level NICU environment for 72 hours while providing multisystemic and multiorgan support, appears to reduce mortality and improve morbidity for newborns with moderate-to-severe HIE.

References

Back, S. A., & Volpe, J. J. (2018). Encephalopathy of prematurity: Pathophysiology. In J. J. Volpe, T. E. Inder, B. T. Darras, L. S. de Vries, A. J. du Plessis, J. J. Neil, & J. M. Perlman (Eds.), *Volpe's neurology of the newborn* (6th ed., pp. 405–424). Philadelphia, PA: Elsevier.

Jacobs, S. E., Morley, C. J., Inder, T. E., Stewart, M. J., Smith, K. R., McNamara, P. J., … Doyle, L. W. (2011). Whole-body hypothermia for term and near-term newborns with hypoxic-ischemic encephalopathy: A randomized controlled trial. *Archives of Pediatrics and Adolescent Medicine, 165*(8), 692–700. doi:10.1001/archpediatrics.2011.43

Simbruner, G., Mittal, R. A., Rohlmann, F., Muche, R., & neo.nEURO. network Trial Participants. (2010). Systemic hypothermia after neonatal encephalopathy: Outcomes of neo.nEURO.network RCT. *Pediatrics, 126*(4), e771–e778. doi:10.1542/peds.2009-2441

Tagin, M. A., Woolcott, C. G., Vincer, M. J., Whyte, R. K., & Stinson, D. A. (2012). Hypothermia for neonatal hypoxic ischemic encephalopathy: An updated systematic review and meta-analysis. *Archives of Pediatrics and Adolescent Medicine, 166*(6), 558–566. doi:10.1001/archpediatrics.2011.1772

PARENT VOICES

Heather McKinnis

When Owen was born at 25 weeks, he was so tiny but so perfect in our eyes. Each ultrasound that first week of his life showed worsening degrees of brain bleeds. When the day 7 scan showed that the bleeding had spread beyond his ventricles and into his brain tissue, we were devastated. By that time, I had read so much about IVH and my one consolation was that his weren't grade IV. I knew what that ultrasound may mean for my child. Bilateral grade IV IVH is the worst bleeds he could have. Our doctors sat us down and went through every single limitation and challenge he may face. They explained the risks over the next weeks and then his delays as he grows. Not once, during those conversations, did one person give us hope. I understand the need for realistic and statistically based information, but as an overwhelmed and terrified first-time mom, I needed someone to give me a glimmer of hope for my baby. That one person was our nurse Barb. After a couple of weeks of stable head ultrasounds and encouraging development from Owen, she encouraged me to just stop anxiously waiting for the bad and to enjoy the good. She told me to watch my baby. He responded to my voice, calmed at my touch, and moved both sides of his body. She reminded me how incredible the brain is and the amazing things she's seen in her time in the NICU. She did not tell me he was going to be OK. She did not give false hope or negative statistics. She held my hand, hugged me when I cried, and helped me find hope in a bleak situation. Owen is now 8 years old. He's healthy, happy, and thriving with his peers. I tell him about Barb often and how she was the first person to see his incredible potential.

ONLINE RESOURCES

National Genetics and Genomics Education Centre. (n.d.). Telling stories: Understanding real life genetics. Retrieved from http://www.tellingstories.nhs.uk

Neuron migration: Illustration of a neuron (a granule cell is a small neuron) migrating along a radial glia. Retrieved from http://www.youtube.com/watch?v=ZRF-gKZHINk

Stanford Medicine. Newborn physical assessment findings. Retrieved from http://med.stanford.edu/newborns/professional-education/photo-gallery.html

University of New South Wales Embryology including animations. (n.d.). *Embryological development of the neurological system*. Retrieved from http://php.med.unsw.edu.au/embryology/index.php?title=Neural_System_Development

Your Genes, Your Health, A Multimedia Guide to Genetic Disorders, DNA Learning Center, Cold Springs Harbor Learning Center.

REFERENCES

Abend, N. S., Jensen, F. E., Inder, T. E., & Volpe, J. J. (2018). Neonatal seizures. In J. J. Volpe, T. E. Inder, B. T. Darras, L. S. de Vries, A. J. du Plessis, J. J. Neil, & J. M. Perlman (Eds.), *Volpe's neurology of the newborn* (6th ed., pp. 275–324). Philadelphia, PA: Elsevier.

Adzick, N. S., Thom, E. A., Spong, C. Y., Brock, J. W., Burrows, P. K., Johnson, M. P., & Farmer, D. L. (2011). A randomized trial of prenatal versus postnatal repair of myelomeningocele. *New England Journal of Medicine, 364*, 993–1004. doi:10.1056/NEJMoa1014379

Alfonso, D. T. (2011). Causes of neonatal brachial plexus palsy. *Bulletin of the NYU Hospital for Joint Diseases, 69*, 11–16. Retrieved from http://hjdbulletin.org/files/archive/pdfs/237.pdf

American Academy of Pediatrics Committee on Genetics. (1999). Folic acid for the prevention of neural tube defects. *Pediatrics, 100*, 143–152. doi:10.1542/peds.104.2.325

American College of Obstetricians and Gynecologists, Committee on Practice Bulletins-Obstetrics. (2017, December). Practice bulletin no. 187: Neural tube defects. *Obstetrics and Gynecology, 130*(6), e279–e290. doi:10.1097/AOG.0000000000002412

Amiel-Tison, C., & Gosselin, J. (2009). Clinical assessment of the infant nervous system. In M. I. Levene & F. A. Chervenak (Eds.), *Fetal and neonatal neurology and neurosurgery* (4th ed., pp. 128–154). Edinburgh, Scotland: Churchill Livingstone/Elsevier.

Au, K. S., Ashley-Koch, A., & Northrup, H. (2010). Epidemiologic and genetic aspects of spina bifida and other neural tube defects. *Developmental Disabilities Research Reviews, 16*(1), 6–15. doi:10.1002/ddrr.93

Back, S. A., & Volpe, J. J. (2018). Encephalopathy of prematurity: Pathophysiology. In J. J. Volpe, T. E. Inder, B. T. Darras, L. S. de Vries, A. J. du Plessis, J. J. Neil, & J. M. Perlman (Eds.), *Volpe's neurology of the newborn* (6th ed., pp. 405–424). Philadelphia, PA: Elsevier.

Balashova O. A., Visina, O., & Borodinsky, L. N. (2018). Folate action in nervous system development and disease. *Developmental Neurobiology, 78*(4), 391–402. doi:10.1002/dneu.22579

Ballabh, P. (2014). Pathogenesis and prevention of intraventricular hemorrhage. *Clinics in Perinatology, 41*(1), 47–67. doi:10.1016/j.clp.2013.09.007

Barks, J. (2008). Technical aspects of starting a neonatal cooling program. *Clinics in Perinatology, 35*(4), 765–776. doi:10.1016/j.clp.2008.07.009

Battin, M. R., Thoresen, M., Robinson, E., Polin, R. A., Edwards, A. D., & Gunn, A. J. (2009). Does head cooling with mild systemic hypothermia affect requirement for blood pressure support? *Pediatrics, 123*(3), 1031–1036. doi:10.1542/peds.2008-1610

Bebbington, M. W., Danzer, E., Johnson, M. P., & Adzick, N. S. (2011). Open fetal surgery for myelomeningocele. *Prenatal Diagnosis, 31(7)*, 689–694. doi:10.1002/pd.2805

Benders, M. J., Groenendaal, F., & de Vries, L. S. (2009). Preterm arterial ischemic stroke. *Seminars in Fetal and Neonatal Medicine, 14(5)*, 272–277. doi:10.1016/j.siny.2009.07.002

Bissinger, R. L., & Annibale, D. J. (2014). *Golden hours: Care of the very low birth weight infant*. Chicago, IL: The National Certification Company

Blackburn, S. T. (2009a). Central nervous system vulnerabilities in preterm infants: Part I. *Journal of Perinatal and Neonatal Nursing, 23*(1), 12–14. doi:10.1097/JPN.0b013e31819685cc

Blackburn, S. T. (2009b). Central nervous system vulnerabilities in preterm infants: Part II. *Journal of Perinatal and Neonatal Nursing, 23*(2), 108–110. doi:10.1097/JPN.0b013e3181a3924b

Blackburn, S. T. (2016). Brain injury in preterm infants: Pathogenesis and nursing implications. *Newborn and Infant Nursing Reviews, 16*(1), 8–12. doi:10.1053/j.nainr.2015.12.004

Blackburn, S. T. (2018). *Maternal, fetal and neonatal physiology: A clinical perspective* (5th ed.). St. Louis, MO: Elsevier.

Bonifacio, S. L., Glass, H. C., Peloquin, S., & Ferriero, D. M. (2011). A new neurological focus in neonatal intensive care. *Nature Reviews. Neurology, 7*, 485–494. doi:10.1038/nrneurol.2011.119

Bonifacio, S. L., Gonzalez, F., & Ferriero, D. M. (2012). Central nervous system injury and neuroprotection. In C. A. Gleason & S. Devaskar (Eds.), *Avery's diseases of the newborn* (pp. 869–891). Philadelphia, PA: Saunders/Elsevier.

Breimer, L. H., & Nilsson, T. K. (2012). Has folate a role in the developing nervous system after birth and not just during embryogenesis and gestation? *Scandinavian Journal of Clinical and Laboratory Investigation, 72*(3), 185–191. 1–7. doi:10.3109/00365513.2012.657230

Brossard-Racine, M., du Plessis, A. J., & Limperopoulos, C. (2015). Developmental cerebellar cognitive affective syndrome in ex-preterm survivors following cerebellar injury. *Cerebellum, 14*(2), 151–164. doi:10.1007/s12311-014-0597-9

Cavalheiro, S., da Costa, M. D. S., Moron, A. F., & Leonard, J. (2017). Comparison of prenatal and postnatal management of patients with myelomeningocele. *Neurosurgery Clinics of North America, 28*(3), 439–448. doi:10.1016/j.nec.2017.02.005

Chabrier, S., Husson, B., Dinomais, M., Landrieu, P., & Nguyen, T. S. (2011). New insights (and new interrogations) in perinatal arterial ischemic stroke. *Thrombosis Research, 127(1)*, 13–22. doi:10.1016/j.thromres.2010.10.003

Cheong, J. L. Y., & Cowan, F. M. (2009). Neonatal arterial ischaemic stroke: Obstetric issues. *Seminars in Fetal and Neonatal Medicine, 14*(5), 267–271. doi:10.1016/j.siny.2009.07.009

Chirinian, N., & Mann, N. (2011). Therapeutic hypothermia for management of neonatal asphyxia: What nurses need to know. *Critical Care Nurse, 31*(3), e1–e12. doi:10.4037/ccn2011873

Chitayat, D., Matsui, D., Amitai, Y., Kennedy, D., Vohra, S., Rieder, M., & Koren, G. (2015). Folic acid supplementation for pregnant women and those planning pregnancy: 2015 update. *The Journal of Clinical Pharmacology, 56*(2), 170–175. doi:10.1002/jcph.616

Christ, L., Barber, J., Murray, A., Dunleavy, M., Stoller, J., Taha, D., . . . Posencheg, M. (2015). Reducing intraventricular hemorrhage in a level III neonatal intensive care unit. *BMJ Quality and Safety, 24*, 731–732. Retrieved from http://qualitysafety.bmj.com/content/24/11/731

Czeizel, A. E., Dudás, I., Paput, L., & Bánhidy, F. (2011). Prevention of neural-tube defects with periconceptional folic acid, methylfolate, or multivitamins? *Annals of Nutrition and Metabolism, 58*, 263–271. doi:10.1159/000330776

Danzer, E., Johnson, M. P., & Adzick, N. S. (2012). Fetal surgery for myelomeningocele: Progress and perspectives. *Developmental Medicine and Child Neurology, 54*(1), 8–14. doi:10.1111/j.1469-8749.2011.04049.x

Danzer, E., Rintoul, N. E., & Adzick, N. S. (2017). Pathophysiology of neural tube defect. In R. A. Polin, S. H. Abman, D. H., Rowitch, W. E. Benitz, & W. W. Fox. (Eds.), *Fetal and neonatal physiology* (5th ed., pp. 1724–1732). Philadelphia, PA: Elsevier Saunders.

Danzer, E., Thomas, N. H., Thomas, A., Friedman, K. B., Gerdes, M., Koh, J., …, & Johnson, M. P. (2016). Long-term neurofunctional outcome, executive functioning, and behavioral adaptive skills following fetal myelomeningocele surgery. *American Journal of Obstetrics and Gynecology, 214*(2), 269.e1–269.e8. doi:10.1016/j.ajog.2015.09.094

Dastgir, J., Chan, K., & Darras, B. (2012). Neonatal hypotonia and neuromuscular disorders. In J. M. Perlman (Ed.), *Neurology* (2nd ed., pp. 237–262). Philadelphia, PA: Saunders/Elsevier.

Dickey, E. J., Long, S. N., & Hunt, R. W. (2011). Hypoxic ischemic encephalopathy—What can we learn from humans? *Journal of Veterinary Internal Medicine, 25*(6), 1231–1240. doi:10.1111/j.1939-1676.2011.00818.x

Ditzenberger, G. R. (2015). Nutritional management. In M. T. Verklan & M. Walden (Eds.), *Core curriculum for neonatal intensive care nursing* (5th ed., pp. 172–196). St. Louis, MO: Saunders/Elsevier.

Doumouchtsis, S., & Arulkumaran, S. (2009). Are all brachial plexus injuries caused by shoulder dystocia? *Obstetrical and Gynecological Survey, 64*(9), 615–623. doi:10.1097/OGX.0b013e3181b27a3a

Doyle, L. W., Crowther, C. A., Middleton, P., Marret, S., & Rouse, D. (2009). Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus. *The Cochrane Database of Systematic Reviews*, (1), CD004661. doi:10.1002/14651858.CD004661.pub3

de Bijl-Marcus, K. A., Brouwer, A. J., de Vries, L. S., & van Wezel-Meijler, G. (2017). The effect of head positioning and head tilting on the incidence of intraventricular hemorrhage in very preterm infants: A systematic review. *Neonatology, 111*, 267–279. doi:10.1159/000449240

de Vries, L. S., & Jongmans, M. J. (2010). Long-term outcome after neonatal hypoxic-ischaemic encephalopathy. *Archives of Disease in Childhood—Fetal and Neonatal Edition, 95*, F220–F224. doi:10.1136/adc.2008.148205

du Plessis, A. J., & Volpe, J. J. (2018). Neural tube development. In J. J. Volpe, T. E. Inder, B. T. Darras, L. S. de Vries, A. J. du Plessis, J. J. Neil, & J. M. Perlman (Eds.), *Volpe's neurology of the newborn* (6th ed., pp. 3–33). Philadelphia, PA: Elsevier.

Epelman, M., Daneman, A., Chauvin, N., & Hirsch, W. (2012). Head ultrasound and MR imaging in the evaluation of neonatal encephalopathy: Competitive or complementary imaging studies? *Magnetic Resonance Imaging Clinics of North America, 20*(1), 93–115. doi:10.1016/j.mric.2011.08.012

Evans, K. N., Hing, A. V., & Cunningham, M. L. (2018). Craniofacial malformations. In C. A. Gleason & S. E. Juul (Eds.), *Avery's diseases of the newborn* (10th ed., pp. 1419–1437). Philadelphia, PA: Elsevier.

Fleiss, B., Stolp. H., Mezger, V., & Gressens, P. (2018). Central nervous system development. In C. A. Gleason & S. E. Juul (Eds.), *Avery's diseases of the newborn* (10th ed., pp. 852–856). Philadelphia, PA: Elsevier.

Fumagalli, M., Bassi, L., Sirgiovanni, I., Mosca, F., Sannia, A., & Ramenghi, L. A. (2015). From germinal matrix to cerebellar haemorrhage. *The Journal of Maternal-Fetal and Neonatal Medicine, 28*(Suppl. 1), 2280–2285. doi:10.3109/14767058.2013.796168

Fyfe, K. L., Yiallourou, S. R., Wong, F. Y., & Horne, R. S. (2014). The development of cardiovascular and cerebral vascular control in preterm infants. *Sleep Medicine Reviews, 18*(4), 299–310. doi:10.1016/j.smrv.2013.06.002

Gancia, P., & Pomero, G. (2011). Brain cooling and eligible newborns: Should we extend the indications? *Journal of Maternal-Fetal and Neonatal Medicine, 24*(Suppl. 1), 53–55. doi:10.3109/14767058.2011.607617

Gano, D. (2016). White matter injury in premature newborns. *Neonatal Network, 35*(2), 73–77. doi:10.1891/0730-0832.35.2.73

Gauda, E. B., & Martin, R. J. (2018). Control of breathing. In C. A. Gleason & S. E. Juul (Eds.), *Avery's diseases of the newborn* (10th ed., pp. 600–617). Philadelphia, PA: Elsevier.

Girard, N., & Raybaud, C. (2011). Neonates with seizures: What to consider, how to image. *Magnetic Resonance Imaging Clinics of North America, 19*(4), 685–708. doi:10.1016/j.mric.2011.08.003

Glass, H. C. (2010). Neurocritical care for neonates. *Neurocritical Care, 12*, 421–429.

Gluckman, P. D., Wyatt, J. S., Azzopardi, D., Ballard, R., Edwards, A. D., Ferriero, D. M., & Gunn, A. J. (2005). Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: Multicentre randomised trial. *The Lancet, 365*, 663–670. doi:10.1016/S0140-6736(05)17946-X

Gomella, T. L., Cunningham, M. D., & Eyal, F. G. (2009). *Neonatology: Management, procedures, on-call problems, diseases, and drugs* (p. 894). New York, NY: McGraw-Hill/Lange.

Gressens, P., & Hüppi, P. S. (2015). Normal and abnormal brain development. In R. J. Martin, A. A. Fanaroff, & M. C. Walsh (Eds.), *Fanaroff and Martin's neonatal-perinatal medicine: Diseases of the fetus and infant* (10th ed., pp. 836–865). Philadelphia, PA: Elsevier Saunders.

Gudsnuk, K. M., & Champagne, F. A. (2011). Epigenetic effects of early developmental experiences. *Clinics in Perinatology, 38(4)*, 703–718. doi:10.1016/j.clp.2011.08.005

Guillet, R., Edwards, A. D., Thoresen, M., Ferriero, D. M., Gluckman, P. D., Whitelaw, A., & Gunn, A. J. (2012). Seven- to eight-year follow-up of the CoolCap trial of head cooling for neonatal encephalopathy. *Pediatric Research, 71*, 205–209. doi:10.1016/j.jpeds.2007.06.003

Gunn, A. J., Wyatt, J. S., Whitelaw, A., Barks, J., Azzopardi, D., Ballard, R., . . . Thoresen, M. (2008). Therapeutic hypothermia changes the prognostic value of clinical evaluation of neonatal encephalopathy. *The Journal of Pediatrics, 152*(1), 55–58.e1. doi:10.1016/j.jpeds.2007.06.003

Gunny, R. S., & Lin, D. (2012). Imaging of perinatal stroke. *Magnetic Resonance Imaging Clinics of North America, 20*(1), 1–33. doi:10.1016/j.mric.2011.10.001

Haines, K. M., Wang, W., & Pierson, C. R. (2013). Cerebellar hemorrhagic injury in premature infants occurs during a vulnerable developmental period and is associated with wider neuropathology. *Acta Neuropathologica Communications, 1*, 69. doi:10.1186/2051-5960-1-69

Heaberlin, P. D. (2019). Neurologic assessment. In E. P. Tappero & M. E. Honeyfield (Eds.), *Physical assessment of the newborn: A comprehensive approach to the art of physical examination* (6th ed., Chapter 11) [Kindle version]. Santa Rosa, CA: NICU Ink.

Hellström-Westas, L., & de Vries, L. S. (2009). EEG and evoked potentials in the neonatal period. In M. I. Levene & F. A. Chervenak (Eds.), *Fetal and neonatal neurology and neurosurgery* (4th ed., pp. 192–221). Edinburgh, Scotland: Churchill Livingstone/Elsevier.

Hirtz, D. G., Weiner, S. J., Bulas, D., DiPietro, M., Seibert, J., Rouse, D. J., . . . Caritis, S. N.; Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. (2015). Antenatal magnesium and cerebral palsy in preterm infants. *The Journal of Pediatrics, 167*, 834–839. doi:10.1016/j.jpeds.2015.06.067

Hockley, A. D., & Solanki, G. A. (2009). Surgical management of neural tube defects. In M. I. Levene & F. A. Chervenak (Eds.), *Fetal and neonatal neurology and neurosurgery* (4th ed., pp. 847–855). Edinburgh, Scotland: Churchill Livingstone/Elsevier.

Hoehn, T., Hansmann, G., Bührer, C., Simbruner, G., Gunn, A. J., Yager, J., & Thoresen, M. (2008). Therapeutic hypothermia in neonates. Review of current clinical data, ILCOR recommendations and suggestions for implementation in neonatal intensive care units. *Resuscitation, 78*(1), 7–12. doi:10.1016/j.resuscitation.2008.04.027

Hoppe, K. K., & Benedetti, T. J. (2018). Complicated deliveries. In C. A. Gleason & S. E. Juul (Eds.), *Avery's diseases of the newborn* (10th ed., pp. 158–169). Philadelphia, PA: Elsevier.

Huang, S. B., & Doherty, D. (2018). Congenital malformations of the central nervous system. In C. A. Gleason & S. E. Juul (Eds.), *Avery's diseases of the newborn* (10th ed., pp. 857–878). Philadelphia, PA: Elsevier.

Inder, T. E., Perlman, J. M., & Volpe, J. J. (2018a). Intracranial hemorrhage: Subdural, subarachnoid, intraventricular (term infant), miscellaneous. In J. J. Volpe, T. E. Inder, B. T. Darras, L. S. de Vries, A. J. du Plessis, J. J. Neil, & J. M. Perlman (Eds.), *Volpe's neurology of the newborn* (6th ed., pp. 593–622). Philadelphia, PA: Elsevier.

Inder, T. E., Perlman, J. M., & Volpe, J. J. (2018b). Preterm intraventricular hemorrhage/posthemorrhagic hydrocephalus. In J. J. Volpe, T. E. Inder, B. T. Darras, L. S. de Vries, A. J. du Plessis, J. J. Neil, & J. M. Perlman (Eds.), *Volpe's neurology of the newborn* (6th ed., pp. 637–698). Philadelphia, PA: Elsevier.

Inder, T. E., & Volpe, J. J. (2018a). Hypoxic-ischemic injury in the term infant: Clinical-neurological features, diagnosis, imaging, prognosis, therapy. In J. J. Volpe, T. E. Inder, B. T. Darras, L. S. de Vries, A. J. du Plessis, J. J. Neil, & J. M. Perlman (Eds.), *Volpe's neurology of the newborn* (6th ed., pp. 510–563). Philadelphia, PA: Elsevier.

Inder, T. E., & Volpe, J. J. (2018b). Intrauterine, intrapartum assessments in the term infant. In J. J. Volpe, T. E. Inder, B. T. Darras, L. S. de Vries, A. J. du Plessis, J. J. Neil, & J. M. Perlman (Eds.), *Volpe's neurology of the newborn* (6th ed., pp. 458–483). Philadelphia, PA: Elsevier.

Inder, T. E., & Volpe, J. J. (2018c). Stroke in the newborn. In J. J. Volpe, T. E. Inder, B. T. Darras, L. S. de Vries, A. J. du Plessis, J. J. Neil, & J. M. Perlman (Eds.), *Volpe's neurology of the newborn* (6th ed., pp. 564–592). Philadelphia, PA: Elsevier.

Jensen, F. E. (2009). Neonatal seizures: An update on mechanisms and management. *Clinics in Perinatology, 36*, 1–20. doi:10.1016/j.clp.2009.08.001

Jett, K., & Friedman, J. M. (2010). Clinical and genetic aspects of neurofibromatosis. *Genetics in Medicine, 12*, 1–11. doi:10.1097/GIM.0b013e3181bf15e3

Johnson, P. J. (2019). Head, eyes, ears, nose, mouth, and neck assessment. In E. P. Tappero & M. E. Honeyfield (Eds.), *Physical assessment of the newborn: A comprehensive approach to the art of physical examination* (6th ed., Chapter 5) [Kindle version]. Santa Rosa, CA: NICU Ink.

Johnston, M. V., Fatemi, A., Wilson, M. A., & Northington, F. (2011). Treatment advances in neonatal neuroprotection and neurointensive care. *The Lancet Neurology, 10*, 372–382. doi:10.1016/S1474-4422(11)70016-3

Joseph, R. A., Killian, M. R., & Brady, E. E. (2017). Nursing care of infants with a ventriculoperitoneal shunt. Advances in Neonatal Care, *17*(6), 430–439. doi:10.1097/ANC.0000000000000439

Juul, S. E., Fleiss, B., McAdams, R. M., & Gressens, P. (2018). Neuroprotection strategies for the newborn. In C. A. Gleason & S. E. Juul (Eds.), *Avery's diseases of the newborn* (10th ed., pp. 910–921). Philadelphia, PA: Elsevier.

Kanekar, S., Kaneda, H., & Shively, A. (2011). Malformations of dorsal induction. *Seminars in Ultrasound, CT, and MRI, 32*(3), 189–199. doi:10.1053/j.sult.2011.02.009

Kanekar, S., Shively, A., & Kaneda, H. (2011). Malformations of ventral induction. *Seminars in Ultrasound, CT, and MRI, 32*(3), 200–210. doi:10.1053/j.sult.2011.02.012

Kelen, D., & Robertson, N. J. (2010). Experimental treatments for hypoxic ischaemic encephalopathy. *Early Human Development, 86*(6), 369–377. doi:10.1016/j.earlhumdev.2010.05.011

Kinney, H. C., & Volpe, J. J. (2018a). Encephalopathy of prematurity: Neuropathology. In J. J. Volpe, T. E. Inder, B. T. Darras, L. S. de Vries, A. J. du Plessis, J. J. Neil, & J. M. Perlman (Eds.), *Volpe's neurology of the newborn* (6th ed., pp. 389–404). Philadelphia, PA: Elsevier.

Kinney, H. C., & Volpe, J. J. (2018b). Myelination events. In J. J. Volpe, T. E. Inder, B. T. Darras, L. S. de Vries, A. J. du Plessis, & J. J. Neil, J. M. Perlman (Eds.), *Volpe's neurology of the newborn* (6th ed., pp. 176–188). Philadelphia, PA: Elsevier.

Kinney, H. C., & Volpe, J. J. (2018c). Organizational events. In J. J. Volpe, T. E. Inder, B. T. Darras, L. S. de Vries, A. J. du Plessis, J. J. Neil, & J. M. Perlman (Eds.), *Volpe's neurology of the newborn* (6th ed., pp. 145–175.). Philadelphia, PA: Elsevier.

Kirton, A., & deVeber, G. (2009). Advances in perinatal ischemic stroke. *Pediatric Neurology, 40(3)*, 205–214. doi:10.1016/j.pediatrneurol.2008.09.018

Kling, P. (1989). Nursing interventions to decrease the risk of periventricular-intraventricular hemorrhage. *Journal of Obstetric, Gynecologic, and Neonatal Nursing, 8*, 462–470. doi:10.1111/j.1552-6909.1989.tb00497.x

Koufman, D., Zanelli, S., Cantey, J. B., & Sanchez, P. J. (2012). Neonatal meningitis: Current treatment options. In J. M. Perlman (Ed.), *Neurology* (2nd ed., pp. 181–202). Philadelphia, PA: Saunders/Elsevier.

Laptook, A. R. (2012). The use of hypothermia to provide neuroprotection for neonatal hypoxic-ischemic brain injury. In J. Perlman (Ed.), *Neurology* (2nd ed., pp. 63–76). Philadelphia, PA: Saunders/Elsevier.

Levene, M., & de Vries, L. S. (2009). Neonatal intracranial hemorrhage. In M. Levene & F. A. Chervenak (Eds.), *Fetal and neonatal neurology and neurosurgery* (4th ed., pp. 395–430). Edinburgh, Scotland: Churchill Livingstone/Elsevier.

Liao, W., Xu, H., Ding, J., & Huang, H. (2018). Mild hypothermia therapy for moderate or severe hypoxic-ischemic encephalopathy in neonates. *Iranian Journal of Public Health, 47*(1), 64–69.

Limperopoulos, C. (2010). Extreme prematurity, cerebellar injury, and autism. *Seminars in Pediatric Neurology, 17*, 25–29.

Limperopoulos, C., du Plessis, A. J., & Volpe, J. J. (2018). Cerebellar hemorrhage. In J. J. Volpe, T. E. Inder, B. T. Darras, L. S. de Vries, A. J. du Plessis, J. J. Neil, & J. M. Perlman (Eds.), *Volpe's neurology of the newborn* (6th ed., pp. 623–636). Philadelphia, PA: Elsevier.

Lista, G., Castoldi, F., Cavigioli, F., Bianchi, S., Fontana, P., & La Verde, A. (2011). Ventilatory management of asphyxiated infant during hypothermia. *Journal of Maternal-Fetal and Neonatal Medicine, 24(Suppl. 1)*, 67–68. doi:10.3109/14767058.2011.607615

Lodygensky, G. A., Menache, C. C., & Hüppi, P. S. (2012). Magnetic resonance imaging's role in the care of the infant at risk for brain injury. In J. M. Perlman (Ed.), *Neonatology* (2nd ed., pp. 285–324). Philadelphia, PA: Saunders/Elsevier.

Long, M., & Brandon, D. H. (2007). Induced hypothermia for neonates with hypoxic-ischemic encephalopathy. *Journal of Obstetric, Gynecologic, and Neonatal Nursing, 36*(3), 293–298. doi:10.1111/j.1552-6909.2007.00150.x

Lori, S., Bertini, G., Molesti, E., Gualandi, D., Gabbanini, S., Bastianelli, M. E., …, Dani, C. (2011). The prognostic role of evoked potentials in neonatal hypoxic-ischemic insult. *Journal of Maternal-Fetal and Neonatal Medicine, 24*, 69–71. doi:10.3109/14767058.2011.607661

Lynch, J. K. (2009). Epidemiology and classification of perinatal stroke. *Seminars in Fetal and Neonatal Medicine, 14*(5), 245–249. doi:10.1016/j.siny.2009.07.001

Madsen, J. R., Frim, D. M., & Hansen, A. R. (2005). Neurosurgery of the newborn. In M. G. McDonald, M. D. Mullett & M. M. Seshia (Eds.), *Avrey's neonatology: Pathophysiology and management of the newborn* (pp. 1410–1427). Philadelphia, PA: Lippincott Williams and Wilkins.

Malusky, S., & Donze, A. (2011). Neutral head positioning in premature infants for intraventricular hemorrhage preventions: An evidence-based review. *Neonatal Network, 30*(6), 381–396. doi:10.1891/0730-0832.30.6.381

McAdams, R. M., & Traudt, C. M. (2018). Brain injury in the term infant. In C. A. Gleason & S. E. Juul (Eds.), *Avery's diseases of the newborn* (10th ed., pp. 897–910). Philadelphia, PA: Elsevier.

Merritt II, J. L., & Gallagher, R. C. (2018). Inborn errors of carbohydrate, ammonia, amino acid and organic acid metabolism. In C. A. Gleason & S. E. Juul (Eds.), *Avery's diseases of the newborn* (10th ed., pp. 232–253). Philadelphia, PA: Elsevier.

Miller, S. P., & Back, S. A. (2017). Pathophysiology of neonatal white matter injury. In R. A. Polin, S. H. Abman, D. H. Rowitch, W. E. Benitz, & W. W. Fox (Eds.), *Fetal and neonatal physiology* (5th ed., pp. 1695–1702). Philadelphia, PA: Elsevier Saunders.

Mineyko, A., & Kirton, A. (2011). The black box of perinatal ischemic stroke pathogenesis. *Journal of Child Neurology, 26*(9), 1154–1162. doi:10.1177/0883073811408312

Moore, K. L., Persaud, T. V. N., & Torchia, M. G. (2015). *The developing human: Clinically oriented embryology* (10th ed.). Philadelphia, PA: Elsevier Saunders.

Mwaniki, M. K., Atieno, M., Lawn, J. E., & Newton, C. R. (2012). Long-term neurodevelopmental outcomes after intrauterine and neonatal insults: A systematic review. *Lancet, 379*(9814), 445–452. doi:10.1016/S0140-6736(11)61577-8

Myers, E., & Ment, L. R. (2009). Long-term outcome of preterm infants and the role of neuroimaging. *Clinics in Perinatology, 36(4)*, 773–790. doi:10.1016/j.clp.2009.07.008

Myers, E., & Ment, L. R. (2012). Perinatal stroke. In J. Perlman (Ed.), *Neurology* (2nd ed., pp. 91–108). Philadelphia, PA: Saunders/Elsevier.

Natarajan, N., & Gospe, S. M., Jr. (2018). Neonatal seizures. In C. A. Gleason & S. E. Juul (Eds.), *Avery's diseases of the newborn* (10th ed., pp. 961–970). Philadelphia, PA: Elsevier.

Neil, J. J., & Inder, T. E. (2018). Neonatal neuroimaging. In C. A. Gleason & S. E. Juul (Eds.), *Avery's diseases of the newborn* (10th ed., pp. 923–951). Philadelphia, PA: Elsevier.

Neil, J. J., & Volpe, J. J. (2018). Encephalopathy of prematurity: Clinical-neurological features, diagnosis, imaging, prognosis, therapy. In J. J. Volpe, T. E. Inder, B. T. Darras, L. S. de Vries, A. J. du Plessis, J. J. Neil, & J. M. Perlman (Eds.), *Volpe's neurology of the newborn* (6th ed., pp. 425–457). Philadelphia, PA: Elsevier.

Orlandi, E., Rossi, C., Perino, A., Cucinella, G., & Orlandi, F. (2016). Prospective sonographic detection of spina bifida at 11-14 weeks and systematic review. *Journal of Maternal-Fetal and Neonatal Medicine, 29*(14), 2363–2367. doi:10.3109/14767058.2015.1085967

Owens, R. (2005). Intraventricular hemorrhage in the premature neonate. *Neonatal Network, 24*(3), 55–71. doi:10.1891/0730-0832.24.3.55

Penn, A. A., Gressens, P., Fleiss, B., Back, S. A., & Gallo, V. (2016). Controversies in preterm brain injury. *Neurobiology of Disease, 92*(Part A), 90–101. doi:10.1016/j.nbd.2015.10.012

Pfister, R., & Soll, R. (2010). Hypothermia for the treatment of infants with hypoxic–ischemic encephalopathy. *Journal of Perinatology, 30*, S82–S87. doi:10.1038/jp.2010.91

Piatt, J. H. (2010). Treatment of myelomeningocele: A review of outcomes and continuing neurosurgical considerations among adults. *Journal of Neurosurgery: Pediatrics, 6*(6), 515–525. doi:10.3171/2010.9.PEDS10266

Pisani, F., & Pavlidis, E. (2018). The role of electroencephalogram in neonatal seizure detection. *Expert Review of Neurotherapeutics, 18*(2), 95–100. doi:10.1080/14737175.2018.1413352

Pitcher, J. B., Schneider, L. A., Drysdale, J. L., Ridding, M. C., & Owens, J. A. (2011). Motor system development of the preterm and low birthweight infant. *Clinics in Perinatology, 38*(4), 605–625. doi:10.1016/j.clp.2011.08.010

Poduri, A., & Volpe, J. J. (2018a). Neuronal development. In J. J. Volpe, T. E. Inder, B. T. Darras, L. S. de Vries, A. J. du Plessis, J. J. Neil, & J. M. Perlman (Eds.), *Volpe's neurology of the newborn* (6th ed., pp. 100–119). Philadelphia, PA: Elsevier.

Poduri, A., & Volpe, J. J. (2018b). Neuronal migration. In J. J. Volpe, T. E. Inder, B. T. Darras, L. S. de Vries, A. J. du Plessis, J. J. Neil, & J. M. Perlman (Eds.), *Volpe's neurology of the newborn* (6th ed., pp. 120–144). Philadelphia, PA: Elsevier.

Pressler, R. M., Boylan, G. B., Marlow, N., Blennow, M., Chiron, C., Cross, J. H., …, Zohar, S. (2015). Bumetanide for the treatment of seizures in newborn babies with hypoxic ischaemic encephalopathy (NEMO): An open-label, dose finding, and feasibility phase 1/2 trial. *The Lancet Neurology, 14*(5), 469–477. doi:10.1016/S1474-4422(14)70303-5

Ramenghi, L. A., & Hüppi, P. S. (2009). Imaging the neonatal brain. In M. I. Levene & F. A. Chervenak (Eds.), *Fetal and neonatal neurology and neurosurgery* (4th ed., pp. 68–102). Edinburgh, Scotland: Churchill/Livingstone/Elsevier.

Rennie, J. M., & Boylan, G. B. (2009). Seizure disorders of the neonate. In M. I. Levene & F. A. Chervenak (Eds.), *Fetal and neonatal neurology and neurosurgery* (4th ed., pp. 698–710). Edinburgh, Scotland: Churchill Livingstone/Elsevier.

Reynolds, R., & Talmage, S. (2011). "Caution! Contents should be cold": Developing a whole-body hypothermia program. *Neonatal Network, 30*(4), 225–230. doi:10.1891/0730-0832.30.4.225

Romantsik, O., Calevo, M. G., & Bruschettini, M. (2017). Head midline position for preventing the occurrence or extension of germinal matrix-intraventricular hemorrhage in preterm infants. *The Cochrane Database of Systematic Reviews*, (7), CD012362 doi:10.1002/14651858.CD012362.pub2

Rutherford, M., Ramenghi, L. A., Edwards, A. D., Brocklehurst, P., Halliday, H., Levene, M., … Azzopardi, D. (2010). Assessment of brain tissue injury after moderate hypothermia in neonates with hypoxic–ischaemic encephalopathy: A nested substudy of a randomised controlled trial. *The Lancet Neurology, 9*(1), 39–45. doi:10.1016/S1474-4422(09)70295-9

Sarkar, S., Barks, J., Bhagat, I., & Donn, S. (2009). Effects of therapeutic hypothermia on multiorgan dysfunction in asphyxiated newborns: Whole-body cooling versus selective head cooling. *Journal of Perinatology, 29*, 558–563. doi:10.1038/jp.2009.37

Sarnat, H., & Sarnat, M. (1976). A clinical and electroencephalographic study. *Archives of Neurology, 33*(10), 696–795. doi:10.1001/archneur.1976.00500100030012

Scher, M. S. (2012). Diagnosis and treatment of neonatal seizures. In J. M. Perlman (Ed.), *Neurology* (2nd ed., pp. 109–141). Philadelphia, PA: Saunders/Elsevier.

Schierholz, E., & Walker, S. R. (2010). Responding to traumatic birth: Subgaleal hemorrhage, assessment, and management during transport. *Advances in Neonatal Care, 10*(6), 311–315. doi:10.1097/ANC.0b013e3181fe9a49

Selway, L. D. (2010). State of the science: Hypoxic-ischemic encephalopathy and hypothermic intervention for neonates. *Advances in Neonatal Care, 10*(2), 60–66. doi:10.1097/ANC.0b013e3181d54b30

Sepulveda, W., Wong, A. E., Sepulveda, F., Alcalde, J. L., Devoto, J. C., & Otayza, F. (2017). Prenatal diagnosis of spina bifida: From intracranial translucency to intrauterine surgery. *Child's Nervous System, 33*(7), 1083–1099. doi:10.1007/s00381-017-3445-7

Shah, D. K., Boylan, G. B., & Rennie, J. M. (2012). Monitoring of seizures in the newborn. *Archives of Disease in Childhood—Fetal and Neonatal Edition, 97*, F65–F69. doi:10.1136/adc.2009.169508

Shetty J. (2015). Neonatal seizures in hypoxic-ischaemic encephalopathy–Risks and benefits of anticonvulsant therapy. *Developmental Medicine and Child Neurology, 57*(Suppl. 3), 40–43. doi:10.1111/dmcn.12724

Silva, M. G., Barros, M. C., Pessoa, U. M., & Guinsburg, R. (2016). Kangaroo-mother care method and neurobehavior of preterm infants. *Early Human Development, 95*, 55–59. doi:10.1016/j.earlhumdev.2016.02.004

Sorem, K., Smith, J. F., & Druzin, M. L. (2009). Antenatal prediction of asphyxia. In M. Levene & F. A. Chervenak (Eds.), *Fetal and neonatal neurology and neurosurgery* (pp. 491–505). Edinburgh, Scotland: Churchill Livingstone/Elsevier.

Stola, A., & Perlman, J. (2008). Post-resuscitation strategies to avoid ongoing injury following intrapartum hypoxia–ischemia. *Seminars in Fetal and Neonatal Medicine, 13*(6), 424–431. doi:10.1016/j.siny.2008.04.011

Sullivan, R., Perry, R., Sloan, A., Kleinhaus, K., & Burtchen, N. (2011). Infant bonding and attachment to the caregiver: Insights from basic and clinical science. *Clinics in Perinatology, 38*(4), 643–656. doi:10.1016/j.clp.2011.08.011

Symes, A. (2016). Developmental outcomes. In M. G. MacDonald & M. M. Seshia (Eds.), *Avery's neonatology: Pathophysiology and management of the newborn* (7th ed., pp. 1157–1168). Philadelphia, PA: Wolters Kluwer.

Tagin, M. A., Woolcott, C. G., Vincer, M. J., Whyte, R. K., & Stinson, D. A. (2012). Hypothermia for neonatal hypoxic ischemic encephalopathy: An updated systematic review and meta-analysis. *Archives of Pediatrics and Adolescent Medicine, 166*(6), 558–566. doi:10.1001/archpediatrics.2011.1772

Takenouchi, T., & Perlman, J. M. (2012). Intraventricular hemorrhage and white matter injury in the preterm infant. In J. Perlman (Ed.), *Neurology* (2nd ed., pp. 27–46). Philadelphia, PA: Saunders/Elsevier.

Tao, J. D., & Mathur, A. M. (2010). Using amplitude-integrated EEG in neonatal intensive care. *Journal of Perinatology, 30*, S73–S81. doi:10.1038/jp.2010.93

Tekes, A., Pinto, P. S., & Huisman, T. A. G. M. (2011). Birth-related injury to the head and cervical spine in neonates. *Magnetic Resonance Imaging Clinics of North America, 19*(4), 777–790. doi:10.1016/j.mric.2011.08.004

Terzis, J. K., & Anesti, K. (2011). Developmental facial paralysis: A review. *Journal of Plastic, Reconstructive and Aesthetic Surgery, 64*(10), 1318–1333. doi:10.1016/j.bjps.2011.04.015

Toet, M. C., & de Vries, L. S. (2012). Amplitude-integrated EEG and its potential role in augmenting management within the NICU. In J. M. Perlman (Ed.), *Neurology* (2nd ed., pp. 263–284). Philadelphia, PA: Saunders/Elsevier.

Trollmann, R., Nüsken, E., & Wenzel, D. (2010). Neonatal somatosensory evoked potentials: Maturational aspects and prognostic value. *Pediatric Neurology, 42*, 427–433. doi:10.1016/j.pediatrneurol.2009.12.007

Uria-Avellanal, C., Marlow, N., & Rennie, J. M. (2013). Outcome following neonatal seizures. *Seminars in Fetal and Neonatal Medicine, 18*(4), 224–32. doi:10.1016/j.siny.2013.01.002

Valiente, M., & Marín, O. (2010). Neuronal migration mechanisms in development and disease. *Current Opinion in Neurobiology, 20*(1), 68–78. doi:10.1016/j.conb.2009.12.003

Vandertak, K. (2009). Cool competence. The nursing challenges of therapeutic hypothermia. *Journal of Neonatal Nursing, 15*(6), 200–203. doi:10.1016/j.jnn.2009.07.011

Verklan, M. T. (2009). The chilling details: Hypoxic-ischemic encephalopathy. *Journal of Perinatal and Neonatal Nursing, 23*(1), 59–68. doi:10.1097/01.JPN.0000346221.48202.7e

Volpe, J. J. (2008). *Neurology of the newborn*. Philadelphia, PA: Elsevier Inc/Saunders.

Volpe J. J. (2018a). Injuries of the extracranial, cranial, intracranial, spinal cord, and peripheral nervous system structures. In J. J. Volpe, T. E. Inder, B. T. Darras, L. S. de Vries, A. J. du Plessis, J. J. Neil, & J. M. Perlman (Eds.), *Volpe's neurology of the newborn* (6th ed., pp. 1093–1125). Philadelphia, PA: Elsevier.

Volpe J. J. (2018b). Neurological examination: Normal and abnormal features. In J. J. Volpe, T. E. Inder, B. T. Darras, L. S. de Vries, A. J. du Plessis, J. J. Neil, & J. M. Perlman (Eds.), *Volpe's neurology of the newborn* (6th ed., pp. 191–221). Philadelphia, PA: Elsevier.

Volpe, J. J., Kinney, H. C., Jensen, F. E., & Rosenberg, P. A. (2011). The developing oligodendrocyte: Key cellular target in brain injury in the premature infant. *International Journal of Developmental Neuroscience, 29*(4), 423–440. doi:10.1016/j.ijdevneu.2011.02.012

Wachtel, E. V., & Hendricks-Muñoz, K. D. (2011). Current management of the infant who presents with neonatal encephalopathy. *Current Problems in Pediatric and Adolescent Health Care, 41*(5), 132–153. doi:10.1016/j.cppeds.2010.12.002

Walker, V. P. (2018). Newborn evaluation. In J. J. Volpe, T. E. Inder, B. T. Darras, L. S. de Vries, A. J. du Plessis, J. J. Neil, & J. M. Perlman (Eds.), *Volpe's neurology of the newborn* (6th ed., pp. 289–311). Philadelphia, PA: Elsevier.

Waller, S. A., Gopalani, S., & Benedetti, T. (2012). Complicated deliveries: Overview. In C. A. Gleason & S. Devaskar (Eds.), *Avery's diseases of the newborn* (pp. 146–158). Philadelphia, PA: Saunders/Elsevier.

Walsh, B. H., Murray, D. M., & Boylan, G. B. (2011). The use of conventional EEG for the assessment of hypoxic ischaemic encephalopathy in the newborn: A review. *Clinical Neurophysiology, 122*(7), 1284–1294. doi:10.1016/j.clinph.2011.03.032

Walsh, B. W., Inder, T. E., & Volpe, J. J. (2017). Intraventricular hemorrhage in the neonate. In R. A. Polin, S. H. Abman, D. H. Rowitch, W. E. Benitz, & W. W. Fox. (Eds.), *Fetal and neonatal physiology* (5th ed., pp. 1333–1349). Philadelphia, PA: Elsevier Saunders.

Watchko, J. F. (2009). Identification of neonates at risk for hazardous hyperbilirubinemia: Emerging clinical insights. *Pediatric Clinics of North America, 56*(3), 671–687. doi:10.1016/j.pcl.2009.04.005

White, K. K., Bouchard, M., & Goldberg, M. J. (2018). Common neonatal orthopedic conditions. In C. A. Gleason & S. E. Juul (Eds.), *Avery's diseases of the newborn* (10th ed., pp. 1438–1449). Philadelphia, PA: Elsevier.

Whitelaw, A., & Aquilina, K. (2009). Neonatal hydrocephalus-clinical assessment and non-surgical treatment. In M. Levene & F. A. Chervenak (Eds.), *Fetal and neonatal neurology and neurosurgery* (4th ed., pp. 819–833). Edinburgh, Scotland: Churchill Livingstone/Elsevier.

Wyatt, J. S., Gluckman, P. D., Liu, P. Y., Azzopardi, D., Ballard, R., Edwards, A. D., . . ., & Gunn A. J.; Group FTCS. (2007). Determinants of outcomes after head cooling for neonatal encephalopathy. *Pediatrics, 119*(5), 912–921. doi:10.1542/peds.2006-2839

Yuskaitis, C. J., & Pomeroy, S. L. (2017). Development of the nervous system. In R. A. Polin, S. H. Abman, D. H., Rowitch, W. E. Benitz, & W. W. Fox. (Eds.), *Fetal and neonatal physiology* (5th ed., pp. 1294–1313). Philadelphia, PA: Elsevier Saunders.

Zanelli, S., Buck, M., & Fairchild, K. (2011). Physiologic and pharmacologic considerations for hypothermia therapy in neonates. *Journal of Perinatology, 31*(6), 377–386. doi:10.1038/jp.2010.146

CHAPTER 16

Auditory System

Kathleen Haubrich

INTRODUCTION

Hearing is a fundamental prerequisite to cognitive, social, and emotional development. Any impairment, either temporary or permanent, from birth to 18 months of age can have a profound effect on the auditory stimulation necessary for early language development (Kennedy et al., 2006). Auditory development, in particular, development of speech, depends on an exposure to a rich acoustic and linguistic environment. Hearing newborns recognize their mothers' voices as they are accustomed to hearing them in utero. Sensory deprivation affects the acquisition of communication skills, even though the hearing loss may be corrected. To prevent or minimize the detrimental effects on social, cognitive, and educational development, hearing impairment must be identified as early as possible (Yoshinaga-Itano, Johnson, Carpenter, & Brown, 2008). A study of childhood language development and academic achievement reported that hearing impairment has a significant impact on the development of a child as evidenced by limited speech. Korver et al. (2010) looked at another aspect of childhood development, namely, receptive and expressive language skills, and found that children with a hearing impairment demonstrated a significant delay in the development of these skills and slower academic achievement.

Approximately 1 to 6 per 1,000 newborns in the United States demonstrate hearing loss (American Speech-Language-Hearing Association [ASHA], 2018b). Risk factors include prematurity and a neonatal intensive care unit stay, among others.

EARLY SCREENING FOR HEARING LOSS

Historically, screening for hearing loss in infants and very young children was limited to observations of behavioral responses to sound such as the ringing of a bell outside of the view of a child. This method was fraught with difficulty and delay in early identification of hearing loss. During the past three decades, great strides have been made toward universal newborn hearing screening (UNHS) through early identification, development of reliable screening programs, consideration of adverse side effects, evaluation of availability and effectiveness, and evaluation of long-term outcomes for earlier diagnosis and interventions (Lim, Kim, & Chung, 2012; Patel & Feldman, 2011; Vohr, 2018). Since the initial Joint Committee Position Statement on Infant Hearing (Joint Committe on Infant Hearing, 1995) through subsequent revisions (Joint Committe on Infant Hearing, 2007; Task Force on Newborn and Infant Hearing, 1999), the American Academy of Pediatrics (AAP) and the U.S. Preventive Services Task Force (USPSTF; Nelson, Bougatsos, & Nygren, 2008), having based recommendations on available evidence, supported the practice of UNHS. UNHS has been widely accepted throughout developed regions of the world with research reports of screening modalities and program evaluation reported through scientific publications (De Capua et al., 2007; Korver et al., 2010; Langagne, Schmidt, Leveque, & Chays, 2008; Ohl, Dornier, Czajka, Chobaut, & Tavernier, 2009; van Dommelen et al., 2010; Verhaert, Willems, Van Kerschaver, & Desloovere, 2008).

ANATOMY OF THE EAR

The ear is the anatomic unit involved in hearing and equilibrium. It consists of three parts: the external ear, the middle ear, and the inner ear. The external ear is composed of the auricle (pinna) and the external ear canal (Figure 16.1). A complex cartilage framework gives structure to the auricle. Because of this anatomic position, the auricle is susceptible to trauma from external forces. The external ear canal is curved posterosuperiorly and anteromedially. The canal is oval in shape, and the long axis is positioned superoinferiorly. Normally, the outer portion of the canal is cartilaginous, and the medial

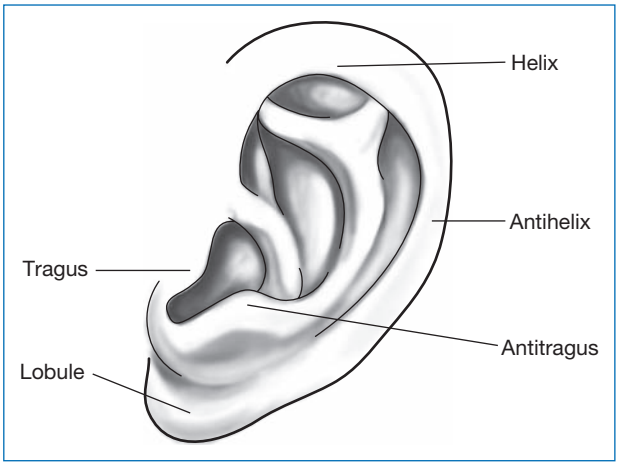

FIGURE 16.1 Anatomy of the external ear.

portion is bony. Before 34 weeks' gestation, the pinna is a slightly formed, cartilage-free double thickness of skin. In the newborn, however, most of the canal is cartilaginous and collapsed (Moore & Linthicum, 2007). However, as ear development ensues, the cartilage becomes firmer, making the outer two-thirds of the canal more patent (Figure 16.2). Cerumen glands and tiny hairs are present in the outer portion of the cartilaginous canal. The medial two-thirds of the canal lie immediately over a bony area and are referred to as the osseous region. The external auditory meatus assumes an irregular path from the concha to the tympanic membrane.

At the termination of the external canal is the eardrum, or tympanic membrane, which forms the boundary between the outer and the middle ear (Figure 16.3). The tympanic membrane has a complicated shape that loosely resembles a flat cone, and moves with changes in air pressure. Because the tympanic membrane is oval and translucent, the middle ear structure often can be visualized through it. The short and long processes of the malleus are attached to the fibrous layer of the tympanic membrane and are visible on the lateral surface. In the middle ear, the malleus, incus, and stapes occupy the region between the tympanic membrane and the oval window of the middle ear. During otoscopic examination, the long process of the incus often can be seen through the tympanic membrane. The middle ear cavity is an air-filled space connected by an air cell system posterior to the mastoid and by the eustachian tube anterior to the nasopharynx. Neither of these is in a dependent position for drainage of fluids. Ciliated columnar cells cover the walls of the tympanic cavity and mastoid air cells. Secretory cells are distributed throughout the middle ear, with the greatest number in the eustachian tube. The stapedius and the tensor muscles of the tympanic membrane attach in the middle ear to the malleus and the stapes by tendons. The chorda tympani nerve passes across the posterior surface. The medial wall of the middle ear cavity contains the oval and round windows. Between these two windows, the lower portion of the cochlea forms a prominence known as the promontorium tympani on the medial wall of the middle ear.

The inner ear consists of a bony labyrinth composed of three parts: the semicircular canals, the vestibule, and the cochlea. A dense, bony capsule in the petrous protein of the temporal bone surrounds these hollow spaces; this capsule contains perilymph and endolymph. Each of the semicircular canals has a dilated portion at the end, referred to as ampulla, which contains the crista ampullaris, a vestibular sense organ. In the vestibule, the utricle and saccules are formed; these structures contain sensory endings important for maintaining equilibrium.

The cochlea is a tubular structure with 2.5 turns; it closely resembles a snail shell, having a base and an apex. The cochlea

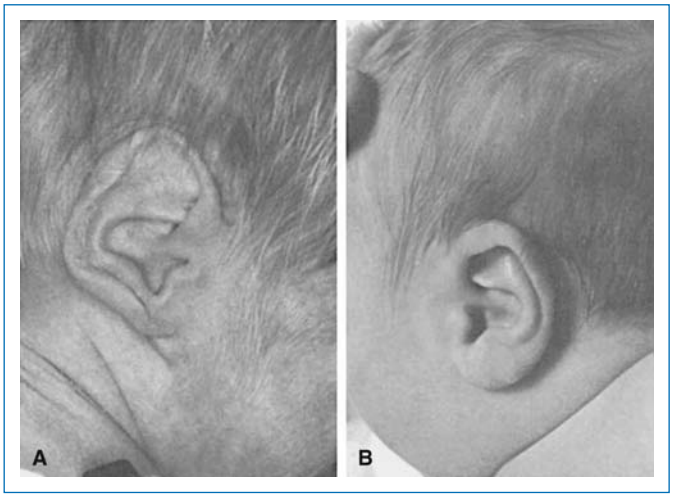

FIGURE 16.2 Premature (A) and full-term (B) ear.

Source: Adapted from Schreiner, R. L., & Bradburn, N. C. (1987). *Care of the newborn* (2nd ed.). New York, NY: Raven Press.

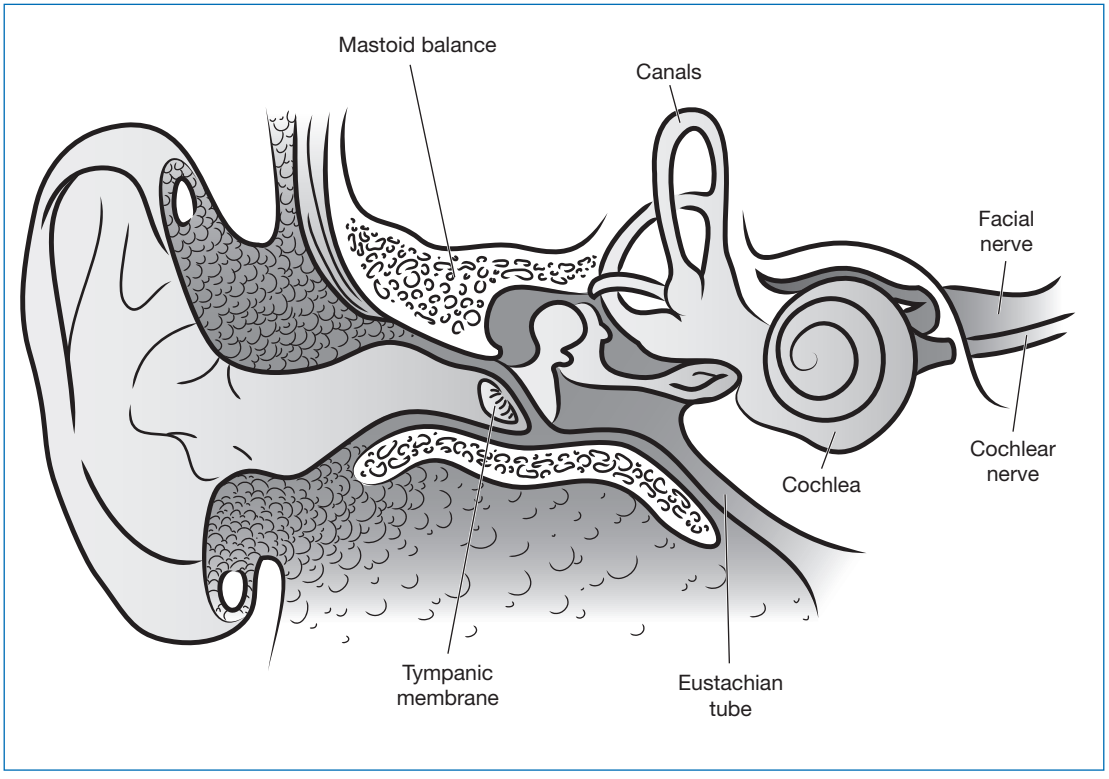

FIGURE 16.3 General framework of the outer, middle, and inner ear.

Source: Redrawn from Pappas, D. (1985). *Diagnosis and treatment of hearing impairment in children.* San Diego, CA: College-Hill Press.

is divided into the scala vestibuli, the scala media, and the scala tympani. The scala vestibuli begins at the oval window, and the scala tympani terminates at the round window. The basilar membrane side of the duct gives rise to the organ of Corti, the organ of hearing. The organ of Corti includes hair cells and supporting cells; attached to the hair cells is a gelatinous membrane called the tectorial membrane.

The membranous labyrinth of the inner ear is composed of connective tissue filled with endolymph that forms in the bony labyrinth. Hair cells of the cochlea and the vestibular labyrinth are attached by afferent nerve fibers to the neurons of the auditory system, the spiral ganglion, and the Scarpa ganglion in the temporal bone. Efferent nerve fibers from ganglia form the auditory and vestibular division of the eighth cranial nerve and exit the temporal bone on its posterior surface to enter the brainstem.

PHYSIOLOGY OF AUDIOLOGIC FUNCTION

External Ear

The external ear consists of the auricle (pinna) and the external auditory meatus (external canal). The primary function of the external ear is to funnel sound to the tympanic membrane. Absence of the auricle contributes to difficulty in sound localization.

Middle Ear

Advancing sound entering the auditory canal directly strikes the tympanic membrane. This membrane and the ossicles serve as transmitters from the outer ear to the inner ear. The malleus, which is continuous with the tympanic membrane and is connected with the incus and stapes, moves the ossicles. Ossicles transfer sound energy into the inner ear through the oval window, which holds the stapes by means of an angular ligament.

The middle ear is lined with respiratory mucosa composed of ciliated columnar epithelial cells, supporting cells, and secretory cells. Secretory cells secrete mucus that forms a complex mucous layer. The cilia of the middle ear interact with the mucus by transporting mastoid and middle ear secretions through the eustachian tube to the nasopharynx, where they are swallowed. This mechanism is known as the mucociliary transport system. Glycoproteins in the mucus determine the viscosity and elasticity of the middle ear mucus. Mucus that is too thick or too thin impedes effective transport of bacteria and cellular debris from the mastoid and middle ear cleft: this transport has a protective effect against ear infections. In addition to serving as an exit for secretions into the nasopharynx, the eustachian tube equalizes the pressure between the middle ear and the ambient atmosphere.

Inner Ear

Before this point in the hearing mechanism, all of the sound energy is contained in the air-filled spaces of the external and middle ear. From the stapes onward, the pathway for sound moves through fluid-filled spaces. When sound is transferred from the tympanic membrane to the inner ear, the stapes creates a fluid wave that is transmitted to the round window. This transmission creates fluid waves that travel from the basal aspect of the cochlea to the apex. As the fluid wave moves, it displaces the basilar membrane. Maximum movement of the basilar membrane occurs at the point specific to the frequency of sound entering the ear; that is, high-frequency sounds cause minimal disturbance at the basal end of the cochlea, and low-frequency sounds cause minimal disturbance at the apex.

Vibrations in the basilar membrane cause movement of the organ of Corti. This organ contains receptor hair cells that are on the basilar membrane. Vibrations of the hair on the hair cells cause either polarization or depolarization, depending on the direction of the bend. When sufficient depolarization occurs, action potentials are produced that are propagated along the auditory pathway to the auditory cortex. The cochlea provides input by coding information about loudness and frequency in the action potentials sent to the cortex, giving meaning to the sound. Hair cells of the spiral organ of Corti are stimulated as they touch the tectorial membrane. Hair cells act as transducers that convert mechanical energy into electrical impulses; this action occurs in the fibers of the spiral ganglion. Axons of these cells become the auditory nerve (vestibulocochlear nerve). Nerve fibers pass to the medulla, the pons, and the midbrain, and finally to the temporal lobes of the cortex, where the impulses are interpreted as sound.

The vestibular system is similar to the auditory system. Fluid moves within the vestibular labyrinth when the head moves. The semicircular canals respond to angular acceleration (rotation), and the utricle and saccule respond to linear acceleration (position). Movement of endolymph exerts force on the hairs of the sensory cells of the cristae and the maculae. Depolarization of the sensory cells produces action potentials, which are transmitted to the vestibular cortex. The vestibular apparatus functions in conjunction with proprioception and visual orientation to maintain balance.

HEARING IMPAIRMENT

The ASHA defines hearing impairment as "a loss of auditory sensitivity that can be measured at birth and for which intervention strategies are known and available." Hearing impairment represents a spectrum of hearing loss classified as mild, moderate, severe, or prolonged.

Types of Hearing Impairment

The types of hearing impairment have been classified according to the location of the problem. Impairment may be one of three types: *conductive*, *sensorineural*, or a *combination* of these. Conductive losses arise from conditions that affect the outer and middle ear; sensorineural loss results from inner ear disorders; and combination losses result from disruptions in both areas of the ear.

Conductive hearing loss exists when dysfunction in the outer or middle ear disrupts the normal sequence of sound localization and vibration. Frequently, the external auditory meatus becomes occluded by cerumen (wax), which impedes the transmission of sound. Otitis media, an infection of the middle ear, is the most common cause of conductive hearing loss. In this instance, fluid accumulates in the middle ear, preventing the tympanic membrane and ossicular chain from vibrating normally (Boudewyns et al., 2011). Congenital deformities of the outer ear also can inhibit the neonate's ability to hear. Because the function of the external ear is to funnel sound, variations in the structure and protrusion of the pinna may contribute to conductive hearing loss. A missing or deformed pinna can result from a malformation of the auricular folds. Atresia of the auditory meatus or abnormal development of the ossicular chain may arise from defective development of the brachial chain (Jones, 2006). Infants with *conductive hearing loss* have difficulty hearing low-frequency sounds (i.e., those in the 125 to 500 Hz range). Management of the neonate with conductive hearing loss is directed toward early observation, detection, and intervention to eliminate the source of infection, to remove the blockage, and to provide amplification, resulting in the restoration of normal hearing.

Sensorineural hearing impairment results from damage to the sensory nerve endings of the cochlea or dysfunction of the auditory nerve (eighth cranial nerve). A typical characteristic of inner ear dysfunction is the inability of the inner ear to interpret fluid

changes in the cochlea. Sensorineural hearing loss may manifest as a congenital inner ear abnormality, resulting in congenital deafness. Other conditions that may cause sensorineural hearing loss are trauma to the inner ear, the effects of certain drugs, prolonged exposure to loud noise, infections, infectious conditions such as measles, and the effects of aging (Harlor & Bower, 2009).

IDENTIFICATION OF THE HEARING-IMPAIRED INFANT

Physical Examination

The physical examination of the infant should be performed in a quiet, warm, draft-free area appropriate for observation and inspection of auditory structures and function. Observing the infant's behavior before examining the ear yields baseline assessments. The alert, normal, full-term newborn reacts by turning toward the sound of human speech or the ring of a bell; this infant also startles to the stimulus of a loud noise. Observation of the preterm infant is deferred to a later time, prior to discharge when the behavioral response has matured. Observation of infant response alone provides only a crude estimate of neonatal hearing ability.

Inspection of the Ear

Inspection of the ear begins with the medial and lateral surfaces of the pinna and the surface of the scalp, face, and neck. Development of the pinna correlates with the infant's gestational age. At term, the pinna of the newborn is well shaped and has sufficient cartilage to maintain normal shape and resistance (Figure 16.2). Before 34 weeks' gestation, the pinna is a slightly formed double thickness of skin. The relationship of the pinna to the other structures of the head and face is important in the initial assessment. With normal placement, the helix is located at the level of the outer canthus and the tragus is roughly level with the intraorbital rim. Low-set auricles frequently are associated with abnormalities of the urinary system. Unilateral conductive hearing loss may be present in children with normal-size pinnae and unilateral absence of the superior crus or in patients with a fused antihelix-helix; thickened, hypertrophied earlobes; a "cup" ear; and a protruding pinna. The pinna may be abnormally small (microtia) or absent (anotia). Atresia (closure of the external auditory canal) may be observed. The condition is classified as mild, indicating a small ear canal; medium, indicating that a bony atretic plate has replaced the canal with ossicular malformation; or severe, indicating a small or absent ear canal and middle ear space.

Several combinations of atresia and microtia may be seen; therefore, all children with these abnormalities should be suspected of having middle ear abnormalities. These infants may also have sensorineural hearing loss. Atresia often is observed with cranial, facial, mandibular, or acrofacial dysostoses. Abnormalities of the skeletal system or chromosomal aberration may also be accompanied by atresia. Aural atresia may be associated with facial, labial, or palatal clefts. Infants with atresia often have conductive hearing loss related to the inability of the ear canal to transmit sound. Preauricular abnormalities, including pits or tags (Figure 16.4) and branchial fistulas, often are accompanied by external or middle ear malformations. These appendages may be present with an otherwise normal-appearing pinna. Preauricular tags or pits usually require only cosmetic surgery or excision if they are draining.

The pinna should be inspected for location and for its relationship to other facial structures. Normal attachment is to the side, level with the middle-third of the face, and fixed in position to the lateral aspect of the external auditory canal. The major

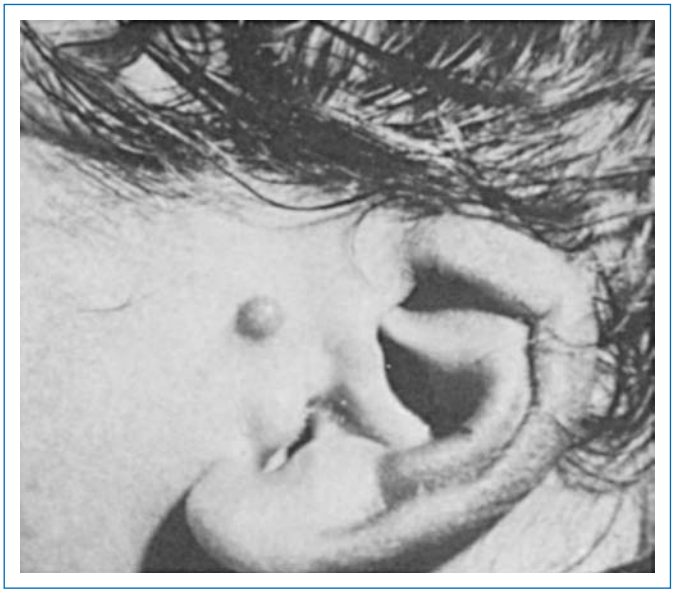

FIGURE 16.4 Preauricular tag.

Source: Adapted from Schreiner, R. L., & Bradburn, N. C. (1987). *Care of the newborn* (2nd ed.). New York, NY: Raven Press.

convolutions of the pinna are the helix, antihelix, tragus, antitragus, and lobule. The lobule of the external ear has no cartilage. The angle of placement of the pinna is almost vertical, and if the angle is more than 10 degrees off normal, it is considered abnormal. The superior helix is located at the outer canthus of the eye, and the tragus is roughly level with the infraorbital rim.

Low-set auricles frequently are associated with other abnormalities of the first and second branchial clefts and with abnormalities of the urinary system. Other abnormalities that may be noted are skin tags, sinuses, or pits, which often are associated with other auditory or renal malformations. The pinna often may be observed to have bruising from a forceps delivery. Depending on the degree of bruising, the discoloration should subside within the first week of life.

The external auditory meatus should then be observed for patency. Atresia or stenosis of the external meatus may be seen. This abnormality results in a conductive hearing loss because sound transmissions are blocked; the condition should be noted as part of the physical findings.

Inspection of the Middle Earand Tympanic Membrane

The depths of the external meatus can be examined with a brightly illuminated pneumatic otoscope. Vernix caseosa frequently is encountered in the ear canal of the neonate. The otoscope is introduced into the ear canal by exerting gentle traction posterosuperiorly on the auricle. In the neonate, the tympanic membrane lies in a nearly horizontal plane. The tympanic membrane is visualized through the collapsed neonatal ear by gently dilating the ear canal with the speculum as the cartilaginous canal is traversed. The tympanic membrane should be examined for thickness, vascularity, and contour. All areas, including the area above the short process of the malleus (pars flaccida), should be visualized for completeness. Normally the tympanic membrane appears translucent. White shadows of the ossicles usually can be seen through the membrane. The mobility of the tympanic membrane can be assessed by applying intermittent pressure through a bulb or by blowing through a polyethylene tube connected to an otoscope.

Otitis media can occur in the first days of life and can be diagnosed by otoscopic examination. Otitis media often manifests as a poorly mobile, bulging, yellow, opacified tympanic membrane. Complications of otitis media are common. Otitis media with middle ear effusion may cause hearing loss, perforation of the tympanic membrane, and possibly intracranial complications, including meningitis, encephalitis, and brain abscess (Vartiainen, 2000). Middle ear effusion occurs in both outpatient and inpatient groups of neonates.

Inspection of the Head and Neck

The anatomy of the head and neck should be assessed for deficits as part of the screening process for all neonates. Ear anomalies associated with head and neck anomalies may occur as a result of a primary regional defect; secondary to a primary defect in an area contiguous to the temporal bone; as part of an inherited defect involving the skeletal system; or as part of a chromosomal disorder. Malformations of the head and neck may be relatively simple or complex. Any neonate with a defect, even a minor one, should be closely examined for hidden major malformations.

Nose. Examination of the nose should be directed toward identification of suspicious defects, such as unusual broadness with a flat base and a short length (saddle nose), small nostrils, and notched alae. Deformities of the nose often appear with other craniofacial abnormalities.

Mouth. Defects in the oral cavity are the most common defect associated with hearing impairment. A child with cleft lip and/or palate has a deficiency in the palate musculature that is primarily related to the inability of the tensor muscle of the velum palatinum to dilate the eustachian tube actively during swallowing. Hearing problems may be observed in patients with cleft palate, depending on the patient's age on examination and the means of the exploration. Cleft lip or palate leaves the child vulnerable to the effusion of fluid and, as a result, to varying degrees of hearing loss. The consequences of effusion raise the rate of otitis media, of which 50% to 90% of incidences have been reported. The hearing loss associated with cleft lip or palate generally is conductive; however, sensorineural and combination losses have been reported. Infants younger than 12 months of age who had cleft palate that was surgically repaired often have a detectable degree of hearing loss. The degree of loss is directly related to the severity of the palatal defect.

Eyes. Deformities of the eyelids are the most common abnormality involving the eyes. A variation in eyelid configuration has been noted in which the upper eyelid forms an almost vertical curve at the level of the medial limit of the cornea and fuses with the lower eyelid. The distance of the two medial angles is increased. These findings typically are noted in Waardenburg syndrome, an autosomal dominant disorder that results in mild to severe sensorineural hearing loss in 50% of patients. The hearing loss may be unilateral or bilateral and progressive.

Epicanthal folds that are true vertical folds extending from the nasal fold into the upper eyelid are commonly noted in infants with Down syndrome, or trisomy 21. Other physical features seen in Down syndrome are low-set ears, small pinnae, and a narrow external ear canal. Infants with this syndrome tend to have recurrent otitis media and anomalies of the middle ear ossicles. The incidence of hearing loss is high, and the condition may be the sensorineural, conductive, or combination type.

Hair. An unusual hair texture or hairline should raise suspicion in the assessment for abnormalities associated with hearing loss. Twisted hair (pili torti) has been associated with sensorineural hearing loss. The hair may be twisted, dry, brittle, or easily broken. Aberrant scalp hair patterns may also be significant.

Neck. Defects of the neck that may be associated with hearing impairment are branchial cleft fistulas and mildly webbed or shortened neck. Not all infants with defects of the head or neck also have hearing impairments; many variations may be observed in the normal neonate population. The presence of such defects does increase the risk of hearing impairment, however, and should be followed up in the long-term interest of the child.

History

The importance of a comprehensive history for identifying the infant at risk cannot be overemphasized. The newborn carries a history extending back to the time of conception and is influenced by both perinatal events and parental genetic composition. Gathering of data on the infant's history is the first step in identifying infants at risk for hearing impairment. A thorough history of familial hearing loss, presenting either at birth or at childhood through adolescence, is significant.

Family History

More than 50 types of hereditary hearing loss have been described. A significant number of hearing impairments may be classified as genetically based. Hereditary hearing loss must be identified on the basis of a thorough medical and family history, which should include the following components:

1. Determination of the cause and circumstances under which the hearing impairment was first noticed: many different circumstances surrounding the onset of the hearing loss may cause it to be labeled as congenital or hereditary, or both. An example of hearing loss that is hereditary and not congenital is Alport syndrome, an autosomal dominant trait resulting in deafness that begins in preadolescence.
2. A complete family history: This should include a history of previous and current pregnancies.
3. An extended family history of data relating to hearing impairments of both immediate and extended family members.
4. A thorough physical examination: The head and neck regions, particularly, should be examined for abnormalities.
5. Selective testing procedures for assessing possible causes of sensorineural hearing loss.

A questionnaire can be used to obtain information on familial hearing loss from the mother. Although the questions easily may be asked orally, the form provides a structure that can ensure consistency and is the preferred method of data gathering in most settings. The questionnaire should be given to all new mothers and should be completed prior to discharge. The questionnaire provides an excellent opportunity for educating the mother on normal speech and language development.

HEREDITARY HEARING LOSS

Autosomal Dominant Inheritance

Autosomal dominant inheritance accounts for 10% to 25% of cases of hereditary hearing impairment. The hearing loss may be unilateral or bilateral, and males and females are affected equally. Autosomal dominant hearing disorders vary in severity ("variable expressivity") and in progression of hearing loss. A typical example of an autosomal dominant hearing disorder occurs in

Waardenburg syndrome, which is characterized by hypertelorism, a high nasal bridge, synophrys, and hypoplastic alae nasi. Pigmentation abnormalities include a white forelock, partial albinism, hypopigmentation of the fundi, blue irises, and premature graying. In this syndrome, severe to profound bilateral sensorineural hearing loss is present with integumentary system involvement. The histopathologic characteristics are absence of the organ of Corti and atrophy of the spiral ganglion.

Another example of an autosomal dominant hearing loss with incomplete penetrance and variable expression occurs in Treacher Collins syndrome. Major features of the syndrome include facial anomalies; small, displaced, or absent external ears; external auditory canal atresia; and poorly developed or malformed tympanic ossicles. Deafness generally is complete and conductive.

Klippel-Feil syndrome, if familial, is another example of autosomal dominance with variable expression. The characteristics of this syndrome are craniofacial disorders, fusion of some or all of the cervical vertebrae, cleft palate (occasionally), and severe sensorineural hearing loss. Crouzon disease is another disorder in which hearing loss is attributed to autosomal dominance with variable expression. An abnormally shaped head, a beaked nose, and marked bilateral exophthalmos caused by premature closure of the cranial sutures characterize this disease. Hearing loss may be conductive because of middle ear deformities or sensorineural abnormalities.

Autosomal Recessive Inheritance

Autosomal recessive inheritance accounts for about 40% of childhood deafness. An estimated one in eight individuals is a carrier for a recessive form of hearing impairment. The incidence of recessive inheritance is higher in marriages of recent common ancestry, such as siblings or cousins. This type of union increases the possibility that each parent will be the carrier of an identical defective gene that may express itself as an abnormal trait. Hearing loss in people with an autosomal recessive gene tends to be more severe than in those with autosomal dominant inheritance, because most cases of recessive hearing loss are associated with the Scheibe deformity of the cochlea. With Scheibe dysplasia, the entire organ of Corti is rudimentary; hair cells are missing, and the supporting cells are distorted or collapsed. The vestibular membrane usually is collapsed. Pendred syndrome, a condition marked by hearing loss and goiter detected in the first 2 years of life, is an example of an autosomal recessive disorder.

X-Linked Disorders. Approximately 3% of hereditary deafness is due to the X-linked mode of transmission (Northern & Downs, 2002). The mutant gene is on the X chromosome, and males transmit only Y chromosomes to their male offspring; therefore, only males are affected. The female is the carrier and has the chance to transmit the gene to 50% of her sons, who manifest the disease, and 50% of her daughters, who carry the abnormality. The hearing loss characteristically is not present at birth but develops in infancy to varying degrees. X-linked hearing losses, with exceptions, are sensorineural, and some retention of hearing in all frequencies often occurs. Recessive, or X-linked, Duchenne muscular dystrophy is an example of this type of disorder. Characterized by muscle wasting, the severe infantile form of muscular dystrophy also is associated with mild to moderate sensorineural hearing loss.

Cytogenetic Disorders. Cytogenetic disorders are caused by structural changes in one or more of the chromosomes or by errors in the distribution of the chromosomes. Down syndrome, which is caused by an extra chromosome 21, is the most common chromosomal aberration syndrome, with an incidence of 1 in 600 to 800 births. Approximately 5% of cases of Down syndrome are due to translocation and fusion of part of chromosome 21 to chromosome 14. Children with trisomy 21 have a high incidence of hearing loss.

Characteristic otologic findings that have an impact on the hearing performance of these children during the early years are a high incidence of (1) stenosis of the external auditory canal, (2) serous otitis media, and (3) a cholesteatoma-persistent growth of squamous epithelium from the ear canal into the middle ear or mastoid through a tear in the tympanic membrane. The narrowed segment is located at the junction of the cartilaginous and bony portions of the canal. With increasing age, the canal has been noted to assume a more typical appearance as the thickened tissue recedes.

The degree of hearing loss in these infants varies, but is rarely profound. On examination of the aperture, some of these children are found to have congenital ossicular malformations and destruction caused by inflammations arising from chronic infection.

Mental retardation is a clinical condition frequently seen with Down syndrome or trisomy 21. The impact of the otologic handicap on the developmental potential of these children is uncertain. **Emergency Alert: Because of the high incidence of hearing loss in this group, early and frequent monitoring is imperative.** Collaborative research studies need to be done to identify factors affecting the otologic problems of infants with Down syndrome and to devise early strategies to optimize these infants' potential (Park, Wilson, Stevens, Harward, & Hohler, 2012).

Differential Diagnosis

No differential diagnosis exists for deafness, although generally a differential diagnosis to determine the etiology of the hearing impairment is listed.

Diagnostic Test

- Laboratory testing is not of benefit in the diagnosis of deafness; however, if a genetic syndrome is suspected, biochemical evidence may be of benefit in determining the etiology.
- Connexin-26 is a genetic marker for deafness (Wang et al., 2011).
- Laboratory testing for perinatal infections such as syphilis, and other toxoplasmosis, other agents, rubella, cytomegalovirus (CMV), and herpes simplex (TORCH) infections may be indicated.
- For bilateral hearing loss, markers for general inflammatory disease, such as sedimentation rate, rheumatoid factor, or 68-kDa protein a marker especially for autoimmune ear disease, may be evaluated.
- CT scanning and MRI may be used to establish a malformation of the cochlea or cochlear nerve. MRI scanning may be used to identify an enlarged vestibular aqueduct, in the case of a sensitive ear in a child with a minor head trauma who presents with deteriorating hearing.

SCREENING METHODS FOR IDENTIFICATION OF HEARING LOSS

Neonatal Hearing Screening is the standard of care in hospitals throughout the United States as well as developed countries worldwide (ASHA, 2018b). The primary focus of hearing screening for neonates (ages 0–6 months) is but one part of a program of comprehensive Early Hearing Detection and Intervention (EHDI)

program of service. The primary focus includes newborn hearing screening as an early identification of infants who are likely to have hearing loss and who will require further evaluation. The secondary purpose is to identify newborns with medical conditions that can present with late-onset hearing loss, to establish for this family unit a plan for continued care monitoring of their child's hearing status (Joint Committee on Infant Hearing, 2007). The EHDI guidelines include hearing screening completion by 1 month of age, diagnosis of a hearing impairment, selection and fitting of a device within 1 month of confirmation of a hearing loss, if parents choose that option, as well as entry into early intervention (EI) services by 6 months of age.

In the past 15 years, programs and procedures for screening newborns have been developed, modified, and improved. The goal of any screening program is to accomplish the task rapidly, accurately, and economically. EHDI refers to the practice of screening every newborn for hearing loss prior to hospital discharge. All 50 states and the District of Columbia have EHDI laws or voluntary compliance programs that screen hearing. The EHDI program is responsible for creating, operating, and continuously improving a system. In addition, institutions are advised to use the risk factors associated with permanent congenital, delayed onset, and/or progressive hearing loss in children. Box 16.1 is a guide to identify infants whose history indicates that degenerative disease or intrauterine infection may cause progressive, fluctuating, or late-onset hearing loss. In these cases, it is recommended that the child have follow-up for 2 years in addition to initial screening.

Box 16.1

RISK FACTORS ASSOCIATED WITH PERMANENT CONGENITAL, DELAYED ONSET, AND/OR PROGRESSIVE HEARING LOSS IN CHILDREN

1. Family history of permanent childhood hearing loss
2. Neonatal intensive care for 2 days or more or any of the following: extracorporeal membrane oxygenation-assisted ventilation, exposure to ototoxic medications (gentamicin and tobramycin) or loop diuretics (furosemide/Lasix), and hyperbilirubinemia requiring exchange transfusion
3. In utero exposure to infections such as CMV, herpes, rubella, syphilis, and toxoplasmosis
4. Craniofacial anomalies, including those that involve the pinna, ear canal, ear tags, ear pits, and temporal bone anomalies
5. Syndromes associated with hearing loss or progressive or late-onset hearing loss, such as Waardenburg, Alport, Pendred, Ushers, and neurofibromatosis
6. Neurodegenerative disorders such as Hunter syndrome
7. Culture-positive postnatal infections associated with sensorineural hearing loss, including confirmed bacterial and viral meningitis
8. Head trauma
9. Chemotherapy
10. Recurrent or persistent otitis media
11. Concerned parent; child may have hearing loss

Source: Adapted from U.S. Preventive Services Task Force. (2008). Universal screening for hearing loss in newborns. U.S. Preventive Services Task Force recommendation statement. *American Family Physician, 122*(1), 143–148. doi:10.1542/peds.2007-2210

The Joint Committee on Infant Hearing (2007) has endorsed universal screening of all newborns. In all cases, before discharge, the parents should be informed about speech and hearing milestones and should be provided with information about community agencies available for long-term follow-up if needed (Figure 16.5).

Peripheral Measurements of Hearing Function

Assessment of hearing function in the neonate has focused on a two-tiered approach in which the evoked otoacoustic emissions (OAEs) test is used initially, and the automated auditory brainstem response (ABR) test is used as follow-up for infants who show hearing impairment on the initial screening. OAEs are low-intensity sounds that can be measured by placing a sensitive microphone in the ear canal. Hearing screening using OAEs is quick, inexpensive, and relatively accurate. Newborns delivered at home, or at birthing centers without hearing screening facilities, need to have some referral mechanism for newborn hearing screening and follow-up mechanism.

If hearing impairment is detected on the OAE test, the ABR test can confirm the validity of that result. The ABR test records the electrical potentials that arise from the auditory nerve system. During this test, disk electrodes are attached to the vertex and mastoid areas, and repetitive sounds are presented to the ear in the form of clicks caused by a direct current pulse. The recorded response is a sequence of waves that represents the action potential of the auditory nerve. The wave latencies in infants at risk tend to show smaller and more prolonged responses. The absolute latency of the ABR waves depends on the intensity of the click stimulus. Reducing the click stimuli from 60 dB to 30–40 dB identifies thresholds of hearing. Absence of all waves indicates the presence of a peripheral lesion.

An abnormal ABR result may be defined as one that shows an absence of response at 40 dB or a wave V latency that exceeds the norm by two standard deviations. Wave V responses are used to determine abnormality because they are highly repeatable in infants and show little variability in normal-hearing subjects. The ABR test appears to be a sensitive method in that no false-negative results have been reported. Considering that any screening method should be quick, inexpensive, and easily administered and should allow easy interpretation of a large number of infants, the drawback to the ABR test is that it is more costly than the OAE test. Nevertheless, the ABR test can be justified as the initial neonatal hearing test, especially in preterm or high-risk infants. The Joint Committee on Infant Hearing (1995, 2007; Task Force on Newborn and Infant Hearing, 1999) specifies that an audiologist should supervise the infant hearing screening program.

In some infants whose initial ABR test results are passing, but the infants meet risk criteria, continuing audiologic follow-up and management may be appropriate as designated by USPSTF for the following 3 years. Those infants include one with risk factors associated with possible progressive or fluctuating loss, such as a family history of progressive hearing loss, CMV infection, and persistent fetal circulation.

Infants who do not demonstrate a repeatable ABR wave V to the signal presented at 40 dB in at least one ear should have a comprehensive hearing evaluation at no later than 6 months of age. This follow-up includes a general physical examination, including examination of the head and neck; otoscopy; identification of relevant physical abnormalities; and laboratory tests for perinatal infections. A comprehensive audiologic evaluation may include additional evoked potential evaluation and acoustic immittance measurements. Although precise data on hearing sensitivity cannot

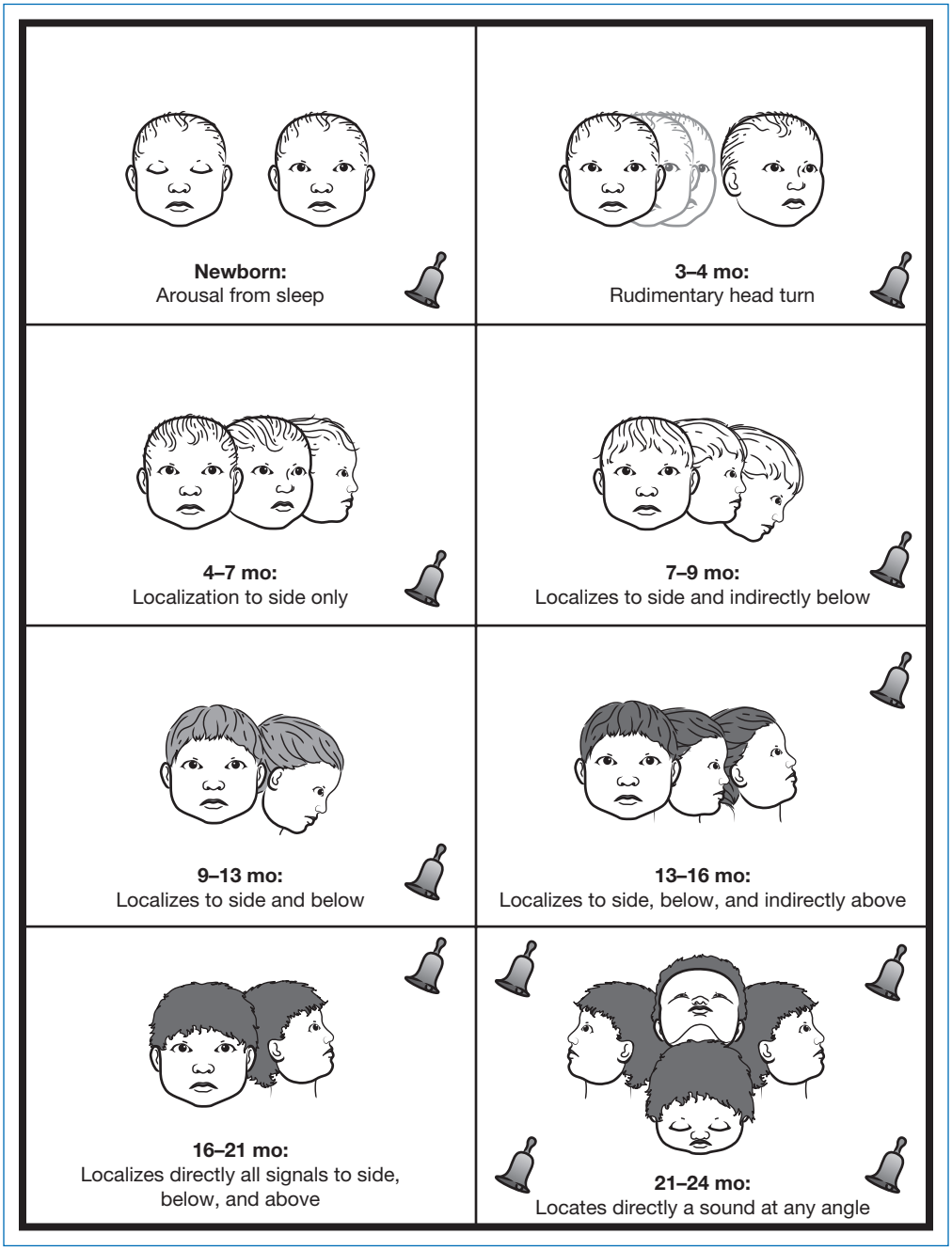

FIGURE 16.5 Maturation of auditory response.

Source: Redrawn from Northern, J. L., & Downs, M. P. (2002). *Hearing in children* (5th ed.). Baltimore, MD: Lippincott Williams & Wilkins.

be obtained until the infant can respond to operant conditioning test procedures at approximately 6 months of age, habilitation should not be delayed.

Infants can be fitted with hearing aids before 3 months of age. Attention to early identification, amplification, and education does not necessarily ensure speech and language acquisition but certainly facilitates it, even in the most profoundly hearing-impaired child.

DEVELOPMENT OF A TREATMENT PLAN FOR THE HEARING-IMPAIRED NEONATE

Hearing screening of all infants should be completed before discharge or no later than 1 month of age. Those who do not pass the newborn screening should undergo audiologic and medical evaluation before 3 months of age for confirmatory testing. If confirmation of a diagnosis is made, then a treatment plan and habilitation can begin. **Quality and Safety: Infants whose history indicates that they are at risk for late-onset hearing loss should be observed by periodic audiologic testing for 3 years.** For the infant with a confirmed hearing loss, efforts are directed at treatment. In accordance with Public Law 99, EI services are (1) evaluation and assessment and (2) development of an individualized family service plan. The full evaluation plan is to be completed within 45 days of referral. This plan may include various methods directed at treatment of serous otitis media, which is a major cause of temporary conductive hearing loss. For the infant with a permanent conductive hearing loss, amplification with a hearing aid may facilitate stimulation in the early critical period. Infants can

be fitted with a hearing aid device as soon as the impairment is diagnosed. In addition to amplification, the family should be taught total communication skills that will enhance interaction between the sender and the receiver. The basic premise is to use every means to communicate, such as gesturing, touching, and attending to stimuli.

The infant with severe to profound hearing impairment who is not at risk for recurrent otitis media and who does not get satisfactory results with a hearing aid is a candidate for cochlear implants (discussed in section "Cochlear Implants"). For the hearing-impaired infant, multiple referral sources exist in which a multidisciplinary approach optimizes the infant's potential for growth and development.

Cochlear Implants

Cochlear implants are not new, but they increasingly are being used to treat infants with severe to profound sensorineural hearing loss. Cochlear implants are electronic devices that are surgically implanted in the inner ear and bypass the damaged part of the ear to deliver electrical signals to the hearing nerve. A cochlear implant system is composed of a microphone, an external sound processor, transmitter, internal cochlear receiver, and electrode array. The external sound processor captures sound with a microphone and converts the sound to digital information. The digital signal is sent to the internal receiver and converted to electrical signals, which stimulate tiny electrodes in the inner ear. The electrodes send the electrical signal to the hearing nerve. These signals are then interpreted by the brain as sound. Implants work only if some spiral ganglion cells are present to transmit the auditory signal. An issue for patients of any age with any type of cochlear implant is the comfortable level of sound. This sometimes is difficult to determine in infants, who cannot provide feedback as to what they are hearing.

Cochlear implants are Food and Drug Administration approved for adults and children as young as 12 months of age. Research has shown that earlier implantation is associated with better speech and language development (Svirsky, Teoh, & Neuburger, 2004). **Quality and Safety: It is critical that infants with hearing loss be diagnosed and early intervention be initiated without delay.** The later the child receives the implants, the more likely it is that speech and language development will be delayed.

Hearing screening is a task for a team of professionals that includes pediatricians, otolaryngologists, audiologists, neurologists, and nurse practitioners. Local public health agencies may provide services such as data collection and referral. Many large metropolitan medical centers have speech and hearing centers as part of a broad base of services ranging from diagnosis to rehabilitation.

Implementation and Evaluation

The multidisciplinary, multiservices approach should be instituted only when all components are available to the infant and the family (ASHA, 2018a). In addition to qualified professionals and services, other factors influence the management and habilitation of the hearing-impaired infant. These factors can facilitate or hamper entry into the system and compliance with the treatment regimen (Box 16.2).

Parental Support

Support for the parents of a hearing-impaired child is based on the foundation of trust and acceptance between the practitioner and the family. Notification of a hearing impairment is an extremely traumatic and deeply disturbing situation for the parents, one that often provokes denial. Often, identification of the problem is delayed because the parents cannot admit that something is wrong. Some practices in the diagnostic workup for hearing impairment seem to favor separation of the parents from the diagnostic process. OAE and ABR testing may foster denial because the findings are abstract, and parents need to have visible, tangible evidence of the impairment. The practitioner plays a major role in reiterating, interpreting, and reinforcing the information conveyed by the audiologist. Sensitivity to the parents' need to grieve the loss of the "perfect child" is important. Acceptance of the handicap can be aided by enlisting the parents as codiagnosticians. Asking the parents what they think the problem is and making them part of the decision-making process objectifies the diagnoses and aids future compliance with the habilitative regimen. Through encouraging dialogue with other parents with similar children's needs and coaching parents with question prompts, the facilitator simulates decision making (Coulter & Ellins, 2007). By listening to the parents' feelings of inadequacy and by indirect teaching, practitioners can help the parents acquire more fruitful coping strategies. Sices, Egbert, and Mercer (2009) investigated parents' and EI specialists' beliefs and experiences regarding discussing child development in primary care. Focus groups were used to collect data from mothers of young children with typical development as well as those who received EI services and specialists. Themes from the data revealed that most mothers preferred a nonalarmist style of communication

Box 16.2

FACTORS INFLUENCING THE MANAGEMENT AND HABILITATION OF THE HEARING-IMPAIRED INFANT

Factors That Facilitate Management and Habilitation

- Acknowledging the parents' sense of loss and feelings of inadequacy: a nonalarmist style of communication
- Interpretation of test results and proposed plan of care
- Information about expected developmental skills, suggestion for promoting skills, and a time frame for follow-up
  Encouragement to seek out and dialogue with other parents of hearing-impaired infants
- Family can be taught total communication skills (gesturing, touching, and attending) to support interaction with the infant.
- Expeditious arrangements for referral
- Parental involvement, offering a wide range of programs that are family-centered focused

Factors That Hamper Management and Habilitation

- Long waiting lists
- Proximity to resources
- Difficulty scheduling appointments
- Parents were unaware of the plan of care.
- Focus should be on the infant sooner, and not the child later.
- Parents wanted more involvement.
- Decision making was therapist centered, not family centered.
- Poor communication between speech and hearing departments

when developmental delays are suspected. Some mothers preferred a more direct approach, including the use of labels to help them understand. The importance of preparation to accept development delays emerged as a theme in all groups. Elements of preparedness included information about expected developmental skills, suggestion for promoting skills, and a time frame for follow-up. The mother–infant relationship is potentially damaged when the infant is hearing impaired. Reciprocal communication that normally occurs between the mother and the infant on an affective and a verbal level has been reported to be diminished with infants who are hearing impaired. The handicapped infant may miss intended signals from parents and may emit signals that are not understood. The parents must capture their infant's visual attention so that their efforts are effectively stimulating. An asynchrony may develop that can retard the infant's ability to acquire language even beyond the limits of the hearing loss itself. The family can be taught total communication skills (gesturing, touching, and attending) to support interaction with the infant.

OUTCOME MEASURES

Outcome measures of the treatment program include early identification and implementation of a comprehensive habilitation plan, in order to maximize communication potential and parental acceptance of the infant's disability. Bailey, Hebbeler, Scarborough, Spiker, & Mallik (2004), in a nationally representative sample of families of children (average age of diagnosis 7.4 months of age) with or at risk for disability, reported very positive first experiences with EI. A small percentage experienced significant delays and wanted more involvement, and nearly 20% were unaware of the existence of a written plan for service. N. W. Pappas, McLeod, McAllister, and McKinnon (2008), in a study of belief in and practice of speech language pathologists in service planning and delivery for children with hearing impairment, revealed that stated beliefs do not always reflect practice: decision making was therapist centered rather than family centered. McCracken and Marsh (2008), in a qualitative study of parental reflections on very early audiologic management, concluded that to be most effective, the focus should be on the infant sooner, rather than on the child later. Ingber, Al-Yagon, and Dromi (2010) examined the actual versus desired family-centered practice in EI for children with hearing loss from the professional and parental viewpoint. Results revealed that parental involvement in the program was perceived positively; however, a wide range of programs needs to be offered for parents.

SUMMARY

On the horizon, as a result of the countless efforts of many, 98% of the babies born in the United States and its territories receive hearing screening in the newborn period (CDC, 2016; NCHAM, 2007). Successful outcomes for children with hearing loss are within reach as a result of advanced knowledge, skills, and hearing technology available to these children and their families. However, only slightly more than half of the infants who do not pass hearing screening receive follow-up diagnostic testing and only a third diagnosed with hearing loss receive intervention by 6 months of age (NCHAM, 2005). Clearly, positive outcomes can only be achieved if babies identified with hearing loss receive appropriate EI services in a timely manner. That is the challenge that lies in the future.

EVIDENCE-BASED PRACTICE BOX

The multidisciplinary, multiservices approach should be instituted only when all components are available to the infant and the family (American Speech-Language-Hearing Association, 2007).

In addition to qualified professionals and services, other factors influence the management and habilitation of the hearing-impaired infant. These factors can facilitate or hamper entry into the system and compliance with the treatment regimen (Box 16.2).

References

American Speech-Language-Hearing Association. (2007). *Childhood apraxia of speech* [Position Statement]. Retrieved from https://www.asha.org/policy/PS2007-00277

Bailey, D. B., Hebbeler, K., Scarborough, A., Spiker, D., & Mallik, S. (2004). First experiences with early intervention: A national perspective. *Pediatrics, 113*(4), 887–896. doi:10.1542/peds.113.4.887

Ingber, S., Al-Yagon, M., & Dromi, E. (2010). Mothers' involvement in early intervention for children with hearing loss: The role of maternal characteristics and context-based perceptions. *Journal of Early Intervention, 32*, 351–369. doi:10.1177/1053815110387066

McCracken, S. G., & Marsh, J. C. (2008). Practitioner expertise in evidence-based practice decision making. *Research in Social Work Practice, 18*, 301–310. doi:10.1177/1049731507308143

Pappas, N. W., McLeod, S., McAllister, L., & McKinnon, D. H. (2008). Parental involvement in speech intervention: A national survey. *Clinical Linguistics and Phonetics, 22*(4/5), 335–344. doi:10.1080/02699200801919737

PARENT VOICES

Keira Sorrells

Aside from having the most wonderfully supportive lactation nurses in our unit, the neonatal therapists were equally incredible. I will never forget when I walked in for a visit and our primary nurse said she had scheduled an appointment for the occupational therapist (OT) to teach me infant massage. This was a highlight of our time in the NICU, where the OT gently coached me and encouraged me to care for my daughter using the healing power of touch. She taught me important cues to look for, as well as potential areas for concern, as we worked together. Being able to provide this type of massage for my girls allowed me an additional manner in which to bond, empowered me to feel more like a "real" mom, and was something I continued to do for my girls on into their toddler years.

ONLINE RESOURCES

American Speech-Language-Hearing Association (ASHA). Retrieved from http://www.asha.org

National Center for Hearing Assessment and Management. Retrieved from http://www.infanthearing.org

National Institute on Deafness and Other Communication Disorders. Retrieved from https://www.nidcd.nih.gov

National Resource Center for Early Detection of Hearing Disorders in Infants. Retrieved from http://www.infanthearing.org

U.S. Preventive Services Task Force. (n.d.). Universal screening for hearing loss in newborns: Recommendation statement. Retrieved from https://www.infanthearing.org/coordinator_orientation/section2/7_unhs_preventative_services.pdf

REFERENCES

American Speech-Language-Hearing Association. (2018a). *Newborn hearing screening* (Practice Portal). Retrieved from https://www.asha.org/Practice-Portal/Professional-Issues/Newborn-Hearing-Screening

American Speech-Language-Hearing Association. (2018b). *The prevalence and incidence of hearing loss in children*. Retrieved from https://www.asha.org/PRPSpecificTopic.aspx?folderid=8589934680&section=Incidence_and_Prevalence

Bailey, D. B., Hebbeler, K., Scarborough, A., Spiker, D., & Mallik, S. (2004). First experiences with early intervention: A national perspective. *Pediatrics, 113*(4), 887–896. doi:10.1542/peds.113.4.887

Boudewyns, A., Declau, F., Van den Ende, J., Van Kerschaver, E., Dirckx, S., Hofkens-Van den Brandt, A., & Van de Heyning, P. (2011). Otitis media with effusion: An underestimated cause of hearing loss in infants. *Otology and Neurotology, 32*(5), 799–804. doi:10.1097/MAO.0b013e31821b0d07

Center for Disease Control and Prevention. (2016). *Data and statistics about hearing loss in children*. Retrieved from https://www.cdc.gov/ncbddd/hearingloss/data.html

Coulter, A., & Ellins, J. (2007). Effectiveness of strategies for informing, educating, and involving patients. *British Medical Journal, 335*(7609), 24–27. doi:10.1136/bmj.39246.581169.80

De Capua, B., Costantini, D., Martufi, C., Latini, G., Gentile, M., & De Felice, C. (2007). Universal neonatal hearing screening: The Siena (Italy) experience on 19,700 newborns. *Early Human Development, 83*(9), 601–606. doi:10.1016/j.earlhumdev.2007.01.001

Harlor, A. D., Jr., & Bower, C. (2009). Hearing assessment in infants and children: Recommendations beyond neonatal screening. *Pediatrics, 124*(4), 1252–1263. doi:10.1542/peds.2009-1997

Ingber, S., Al-Yagon, M., & Dromi, E. (2010). Mothers' involvement in early intervention for children with hearing loss: The role of maternal characteristics and context-based perceptions. *Journal of Early Intervention, 32*(5), 351–369. doi:10.1177/1053815110387066

Joint Committe on Infant Hearing. (1994). Joint committee on infant hearing 1994 position statement. *Pediatrics, 95*, 152–156. Retrieved from https://pediatrics.aappublications.org/content/95/1/152

Joint Committee on Infant Hearing. (2007). Year 2007 position statement: Principles and guidelines for early hearing detection and intervention programs. *Pediatrics, 120*(4), 898–921. Retrieved from https://www.infanthearing.org/resources/2007_JCIH.pdf doi:10.1542/peds.2007-2333

Jones, K. L. (2006). *Smith's recognizable patterns of human malformation* (6th ed.). Philadelphia, PA: Elsevier, Saunders.

Kennedy, C. R., McCann, D. C., Campbell, M. J., Law, C. M., Mullee, M., Petrou, S., . . . Stevenson, J. (2006). Language ability after early detection of permanent childhood hearing impairment. *The New England Journal of Medicine, 354*(20), 2131–2141. doi:10.1056/NEJMoa054915

Korver, A. M., Konings, S., Dekker, F. W., Beers, M., Wever, C. C., Frijns, J. H., & Oudesluys-Murphy, A. M. (2010). Newborn hearing screening vs later hearing screening and developmental outcomes in children with permanent childhood hearing impairment. *The Journal of the American Medical Association, 304*(15), 1701–1708. doi:10.1001/jama.2010.1501

Langagne, T., Schmidt, P., Leveque, M., & Chays, A. (2008). Universal hearing screening in the Champagne-Ardenne regions: Results and consideration after 55,000 births from January 2004 to June 2007. *Revue de Laryngologie—Otologie—Rhinologie, 129*(3), 153–158. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/1969415

Lim, H. W., Kim, E. A., & Chung, J. W. (2012). Audiological follow-up results after newborn hearing screening program. *Clinical and Experimental Otorhinolaryngology, 5*(2), 57–61. doi:10.3342/ceo.2012.5.2.57

McCracken, S. G., & Marsh, J. C.(2008). Practitioner expertise in evidence-based practice decision making. *Research in Social Work Practice, 18*(4), 301–310. doi:10.1177/1049731507308143

Moore, J. K., & Linthicum, F. H., Jr. (2007). The human auditory system: A timeline of development. *International Journal of Audiology, 46*(9), 460–478. doi:10.1080/14992020701383019

National Center for Hearing Assessment and Management. (2007). *Universal newborn hearing screening: Summary statistics of UNHS in the United States*.

National Center for Hearing Assessment and Management. (2008). *Loss to follow-up threatens success of newborn hearing screening programs*. Retrieved from https://www.infanthearing.org/coordinator_orientation/section13/46_follow_up.pdf

Nelson, H. D., Bougatsos, C., & Nygren, P. (2008). Universal newborn hearing screening: Systematic review to update the 2001 US preventive services task force recommendation. *Pediatrics, 122*(1), e266–e276. doi:10.1542/peds.2007-1422

Northern, J. L., & Downs, M. P. (2002). *Hearing in children* (5th ed.). Baltimore, MD: Lippincott Williams & Wilkins.

Ohl, C., Dornier, L., Czajka, C., Chobaut, J. C., & Tavernier, L. (2009). Newborn hearing screening on infants at risk. *International Journal of Pediatric Otorhinolaryngology, 73*(12), 1691–1695. doi:10.1016/j.ijporl.2009.08.027

Pappas, D. (1985). *Diagnosis and treatment of hearing impairment in children*. San Diego, CA: College-Hill Press.

Pappas, N. W., McLeod, S., McAllister, L., & McKinnon, D. H. (2008). Parental involvement in speech intervention: A national survey. *Clinical Linguistics and Phonetics, 22*(4–5), 335–344. doi:10.1080/02699200801919737

Park, A. H., Wilson, M. A., Stevens, P. T., Harward, R., & Hohler, N. (2012). Identification of hearing loss in pediatric patients with Down syndrome. *Otolaryngology-Head and Neck Surgery, 146*(1), 135–140. doi:10.1177/0194599811425156

Patel, H., & Feldman, M. (2011). Universal newborn hearing screening. *Paediatrics and Child Health, 16*(5), 301–310. doi:10.1093/pch/16.5.301

Schreiner, R. L., & Bradburn, N. C. (1987). *Care of the newborn* (2nd ed.). New York, NY: Raven Press.

Sices, L., Egbert, L., & Mercer, M. B. (2009). Sugar-coaters and straight talkers: Communicating about developmental delays in primary care. *Pediatrics, 124*(4), e705–e713. doi:10.1542/peds.2009-0286

Svirsky, M. A., Teoh, S. W., & Neuburger, H. (2004). Development of language and speech perception in congenitally, profoundly deaf children as a function of age at cochlear implantation. *Audiology and Neurotology, 9*(4), 224–233. doi:10.1159/000078392

Task Force on Newborn and Infant Hearing. (1999). Newborn and infant hearing loss: Detection and intervention. *Pediatrics, 103*(2), 527–530. doi:10.1542/peds.103.2.527

U.S. Preventive Services Task Force. (2008). Universal screening for hearing loss in newborns. U.S. Preventive Services Task Force recommendation statement. *American Family Physician, 122*(1), 143–148. doi:10.1542/peds.2007-2210

van Dommelen, P., Mohangoo, A. D., Verkerk, P. H., van der Ploeg, C. P., van Straaten, H. L., & The Dutch NICU Neonatal Hearing Screening Working Group. (2010). Risk indicators for hearing loss in infants treated in different neonatal intensive care units. *Acta Paediatrica, 99*(3), 344–349. doi:10.1111/j.1651-2227.2009.01614.x

Vartiainen, E. (2000). Otitis media with effusion in children with congenital or early-onset hearing impairment. *Journal of Otolaryngology, 29*(4), 221–223. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/11003073

Verhaert, N., Willems, M., Van Kerschaver, E., & Desloovere, C. (2008). Impact of early hearing screening and treatment on language development and education level: Evaluation of 6 years of universal newborn hearing screening (ALGO®) in Flanders, Belgium. *International Journal of Pediatric Otorhinolaryngology, 72*(5), 599–608. doi:10.1016/j.ijporl.2008.01.012

Vohr, B. R. (2018). Screening the newborn for hearing loss. In M. S. Kim (Ed.), *UpToDate*. Retrieved from https://www.uptodate.com/contents/screening-the-newborn-for-hearing-loss

Wang, Q. J., Zhao, Y. L., Rao, S. Q., Guo, Y. F., He, Y., Lan, L., . . . Shen, Y. (2011). Newborn hearing concurrent gene screening can improve care for hearing loss: A study on 14,913 Chinese newborns. *International Journal of Pediatric Otorhinolaryngology, 75*(4), 535–542. doi:10.1016/j.ijporl.2011.01.016

Yoshinaga-Itano, C., Johnson, C. D. C., Carpenter, K., & Brown, A. S. (2008, May). Outcomes of children with mild bilateral hearing loss and unilateral hearing loss. In *Seminars in Hearing* (Vol. 29, No. 02, pp. 196–211). New York, NY: Thieme Medical Publishers.

CHAPTER 17

Ophthalmic System

Lori Baas Rubarth and Debra M. Parker

INTRODUCTION

Newborn eyes begin to develop during intrauterine life, making them susceptible to malformation, deformation, and disruption injuries. Congenital anomalies, congenital infections, and prematurity can affect visual acuity, which can lead to blindness. In addition, other maternal or neonatal diseases can affect the eyes. Therefore, early detection and treatment of eye disorders are essential for the best possible outcome.

This chapter outlines the embryologic development of the eye, reviews the methods of assessment of a newborn's eyes, describes specific ophthalmic disorders of the eye, and describes diseases that can affect the eyes, including prematurity. Nursing care of the patient and family will be discussed.

EMBRYOLOGY

Eye development has its beginnings during early embryogenesis with the formation of a single eye field in the neural plate (Schoenwolf, Bleyl, Brauer, & Francis-West, 2015). Many transcription factors early in development regulate and induce eye development. Without these transcription factors and other enzymes or proteins, anomalies can occur. The initial single eye field is stimulated by the sonic hedgehog protein to split into two separate optic fields. Without this early splitting stimulation, holoprosencephaly (failure of brain to split into two hemispheres) and cyclopia (a single, midline eye) would occur (Schoenwolf et al., 2015). Lack of transcription factors leads to anomalies like anophthalmia (absence of the eye) or microphthalmia (small eye).

The eye develops from the following embryonic tissues: ectoderm, neuroectoderm, neural crest cells, and mesoderm. The lens develops from the ectoderm during the fifth to seventh week. The cornea develops from the ectoderm and mesoderm. The pigmented epithelium and part of the retina develop from the neuroectoderm. The ciliary and iris muscles, part of the choroid, and the sclera develop from neural crest cells. Part of the choroid also develops from the mesoderm (Figure 17.1).

At about 22 days after fertilization, lateral grooves form, which mark the early placement of the eyes in the embryo (Schoenwolf

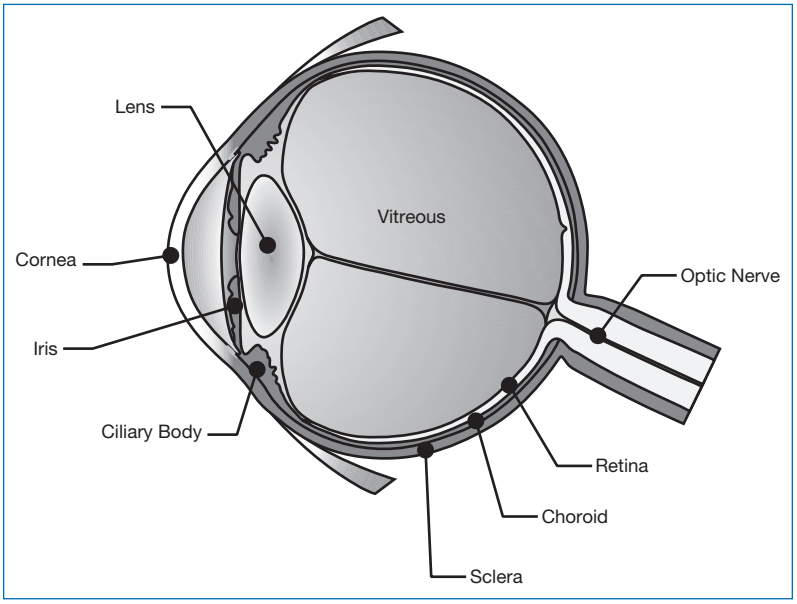

FIGURE 17.1 Anatomy of the eye.

et al., 2015). Bilateral invaginations of the neural tube occur with formation of the optic vesicles. These two optic vesicles remain in contact with the developing brain. By about 32 to 34 days, the optic vesicles change shape to appear as a "goblet" with an additional invagination of the ectoderm inward becoming the lens of the eye (Schoenwolf et al., 2015, p. 490). The fibers within the lens become transparent with the assistance of crystallins, which are soluble proteins within the eye. With the invagination of the optic cup, there are two layers formed, which develop into the inner retina containing rods and cones and the outer melanin containing pigmented epithelium. These two layers of the retina do not fuse completely, but can separate, causing a retinal detachment with many types of trauma to the head. Both layers expand over the lens from the edges of the optic cup, becoming the iris. The color of the iris is either light blue or gray at birth but becomes fully developed with increased pigment by about 6 months of age.

Cellular differentiation and development continues within the eye throughout fetal life. Macular differentiation occurs during the sixth month, and the fovea centralis, the area needed for sharp, high-acuity vision, does not mature until months into the postpartum period (Schoenwolf et al., 2015). Therefore, the term newborn's vision is present, but limited during the first few days and weeks of life. Newborns are most interested in high-contrast shapes that are about 8 to 12 inches from the eyes.

The eyelids develop as surface ectoderm folds over the cornea by about the sixth week of fetal life. The eyelids fuse together by the eighth week, but separate again sometime between the fifth and seventh months of fetal life. The lacrimal glands form from the ectoderm, but are still immature until about 6 weeks after birth (Schoenwolf et al., 2015). Tear production in newborns is limited until that time.

ASSESSMENT AND EXAMINATION TECHNIQUES

History

With an evaluation of the eye, it is important to understand the background of neonatal eye disorders (see Other Disorders That Affect the Eyes). Understanding of these disorders can assist the nurse in determining whether there are any risk factors for eye problems, for example, maternal diabetes, prematurity, alcohol consumption, or congenital diseases. The nurse can question the parents or view the maternal medical record to determine known family, maternal, or perinatal risk factors associated with vision problems. The nurse should look specifically for exposure to infectious diseases such as gonorrhea, chlamydia, rubella, or cytomegalovirus (CMV), which are known to cause significant eye problems in newborns. The nurse should also look at the perinatal history for signs of hypoxia or anoxia (e.g., low Apgar score), as well as conditions associated with possible damage to the brain including vision. Parents who have had a previous preterm birth may already have knowledge or experience with retinopathy of prematurity (ROP). Nurses also need to understand the terminology involved in assessment of the newborn eye (Table 17.1).

Examination

After birth, a screening examination of the eye is indicated. A full eye examination is not practical or indicated unless the newborn presents with some eye pathology. A knowledge of eye anatomy is important as you examine the eye (Figure 17.1). For a newborn screening examination, the external eye, eyelids, pupillary

TABLE 17.1

NEWBORN EYE ASSESSMENT TERMINOLOGY

Definitions	
Amblyopia	Known as "lazy eye" where one eye wanders from a straight line of vision
Aniridia	Much or all of the iris is missing
Anisometropia	A major difference in refractive error between the eyes
Anophthalmos	Complete absence of the ocular tissue within the orbit
Antimongoloid slant	An inner canthus that is higher than the outer canthus
Blennorrhea	Excessive mucus discharge from the eye
Brushfield spots	Speckled iris; frequently associated with Down syndrome
Coloboma	Defect or opening that results from failure of part of the eye to close during embryogenesis; can occur in the iris or eyelids
Ectropion	A condition in which the eyelid is turned outward
Endophthalmitis	Inflammation of the internal eye tissues and fluid
Epicanthal fold	Skin that appears to overlap and partially obscure the inner canthus
Epiphora	Excessive tearing
Esotropia	Inward deviation of the eyes—presents as "cross-eyed"
Exophthalmos	An eye that appears to be bulging
Exotropia	Outward deviation of the eyes
Heterochromia	Pigmentation of the two irises is different
Hyperopia	Farsighted
Hypertelorism	Increased interorbital distance or wide space between the eyes
Inner canthus	The angle of the eyelid nearest the nose

(*continued*)

TABLE 17.1

NEWBORN EYE ASSESSMENT TERMINOLOGY (*continued*)

Definitions	
Interpupillary distance	The distance between the centers of each pupil
Leukocoria	"White" reflex, instead of red
Microphthalmia/ microphthalmos	Small eyes
Mongoloid slant	An outer canthus that is higher than the inner canthus
Myopia	Nearsightedness
Nystagmus	The involuntary rhythmic or oscillating movements of the eyes
Outer canthus	The outer angle of the eyelid
Palpebral fissure (width)	Width of the eyelid opening from inner canthus to outer canthus (fissure = opening)
Proptosis	Bulging of the eyes (exophthalmos)
Ptosis	Drooping of the upper eyelid
Strabismus	Cross-eyed; a condition where the eyes aim in different directions
Synophrys	An abnormal extension of the eyebrows so that they meet in the middle (midline)

response, and red reflex are the major components. During the examination, the newborn should be quiet, awake, and alert. Dimming the lights or a darkened room will assist with the pupillary assessment and the parts of the examination. Holding the infant upright can facilitate spontaneous opening of the eyes. It is important to protect the eye from injury and still evaluate as much of the eyes as possible. This requires a gentle opening of the eyes without stress on the infant and without scratching of the eyes. One hand is usually used to open the eyelids with two fingers, while the other hand holds the ophthalmoscope or light source. A second examiner is helpful during an examination of the eyes. Premature infant eye examinations may be delayed until approximately 32 weeks' gestation or longer for evaluation of the pupils and retina.

External Eye. Examination of the external features of the eye begins with inspection. Newborn eyes are examined for shape, symmetry, and size, as well as the presence of eyebrows and eyelashes. The eyes should appear clear, symmetric in size, and without discharge.

Eyelids. The eyelids are examined for movement, redness, swelling, colobomas, or other abnormalities. Infants with an inability to

TABLE 17.2

EXTERNAL EYE DIMENSIONS (TERM NEWBORN)

Interpupillary distance	33–46 mm (average 39 mm)
Inner canthal distance	13–26 mm (average 20 mm)
Palpebral width (medial to lateral canthus)	17–22 mm (average 18 mm)
Pupil size	2–4 mm
Cornea	9–10 mm

Sources: Adapted from Jones, K. L., Jones, M. C., & Casanelles, M. D. C. (2013). Normal standards—Facial measurements. In K. L. Jones, M. C. Jones, & M. del Campo (Eds.), *Smith's recognizable patterns of human malformation* (7th ed., pp. 933f–936f). Philadelphia, PA: Elsevier Saunders; Örge, F. H., & Grigorian, F. (2015). The eye—Part 1: Examination and common problems of the neonatal eye. In R. J. Martin, A. A. Fanaroff, & M. C. Walsh (Eds.), *Fanaroff & Martin's neonatal-perinatal medicine: Diseases of the fetus and infant* (10th ed., Table 103-2). Philadelphia, PA: Elsevier Saunders; and Scanlon, J. W., Nelson, T., Grylack, L. J., & Smith, Y. F. (1979). *A system of newborn physical examination.* Baltimore, MD: University Park Press.

open their eyelids or who have ptosis (drooping) of one or both eyelids can develop amblyopia and poor visual development. Infants must be able to view images on the retina during the first months of life for normal vision to occur (Pineles & Isenberg, 2016). Deprivation amblyopia due to drooping eyelids can lead to poor vision. The presence of unusual folds (e.g., epicanthal folds near the inner canthus) and the slant of the eye (upward or downward) should be noted.

Pupils. The pupils are examined for size, shape, symmetry, and reaction to light. An examination with an ophthalmoscope is indicated to check for red reflex. The color, clarity, and intensity of the red reflex should be checked and compared bilaterally. In dark-skinned infants, the red reflex may be more of a pale orange or gray rather than red (Johnson, 2015). It can be difficult to obtain a red reflex on premature infants under 28 weeks' gestation due to cloudy corneas, cloudy vitreous, and vasculature of the lens. A "white" reflex (leukocoria) would indicate a blockage of light getting to the retina. The differential diagnosis of leukocoria includes cataract, retinoblastoma, persistent hyperplastic primary vitreous, retinal detachment, ROP, uveitis, Peter's anomaly, and Coats' disease (Cagini, Tosi, Stracci, Rinaldi, & Verotti, 2017; de Alba Campomanes & Binenbaum, 2018). If dark spots are noted, this could be due to cataracts, retinal damage, or hemorrhage. A significant variation between the two eyes would need further retinal assessment. The onset of pupillary constriction in response to light is present by about 30 to 34 weeks' gestation. Interpupillary distance and pupil size can also be assessed (Table 17.2).

Cornea. The cornea is the clear layer covering the pupil and is examined for clarity and size (Table 17.2). **Emergency Alert: A cloudy cornea may be caused by congenital glaucoma, errors of metabolism, or congenital corneal dystrophy. This condition is almost always indicative of a serious eye problem.** Trauma at birth can result in injury to the cornea, giving the cornea a hazy appearance. Preterm infants may also have a transient haziness of the cornea during the first week of life.

Iris and Lens. The iris is examined for coloboma and color. The iris or eye color of dark-skinned Caucasian and African American infants is often darker due to earlier melanin deposition. The deposition of color in most infant eyes occurs by 6 months of age. Heterochromia is a color variation, where the two eyes are of different colors or it can be that there are two colors within the same eye. **Quality and Safety: Heterochromia can be a clue to the development of other disorders, including Sturge–Weber syndrome (with port-wine stain), Waardenburg syndrome, or Hirschsprung disease, and would indicate the need for further follow-up** (de Alba Campomanes & Bineebaum, 2018). The iris is examined for coloboma resembling a keyhole within the pupil. The presence of coloboma may also indicate a need to look for abnormalities in other systems also, for example, fetal alcohol syndrome (FAS). Infants with FAS can have colobomas, cataracts, and microphthalmos. The presence of these findings should alert the nurse to look for other features of the syndrome. The maternal history should also be reevaluated for alcohol use during the pregnancy.

The lens is located behind the iris. A cataract results in cloudiness or a white, opaque lens. A pediatric ophthalmologist needs to evaluate any cataract found in a newborn as soon as possible to determine if it is visually significant. Surgery would be performed to remove vision-threatening cataracts as soon as possible.

Sclera. The sclera is examined for color and hemorrhages. The sclera of term infants should be white in color. The infant sclera can take on a bluish white appearance in the premature infant due to the thinness of the sclera. **Quality and Safety: In term infants, a blue sclera is indicative of possible osteogenesis imperfecta.** Subconjunctival hemorrhages are frequently visualized on the sclera of normal, healthy term infants following a vaginal delivery due to the pressure changes throughout the birthing process. They present no significant long-term complication for these infants.

Eye Movements. It is also important to note the infant's eye movements during the examination. In the neonate, the location or position of the eyes varies with immaturity and/or activity. Many infants display deviations in eye movements, exhibiting exotropia, esotropia, or nystagmus (Table 17.1). These are types of eye wandering or twitching movements of the eye that occur in almost all infants and are considered normal. These eye movements should disappear within the first few months of life. Any persistent deviation needs to be evaluated.

Vision. The infant's vision can also be assessed immediately after birth. Infants will look around at objects in the environment. Newborns can follow an object when placed in front of them. A term newborn's vision is immature. Determining a newborn's visual acuity cannot be done easily and will not be discussed as an examination method in this textbook. But understanding of the infant's vision progression is necessary for caring for these infants. All newborns are born with some degree of myopia or nearsightedness and appear to see best at about 8 to 10 inches from their faces. Infants appear to enjoy highly contrasted (black and white) objects, especially faces in the environment (A. M. Brown, Lindsey, Cammenga, Giannone, & Stenger, 2015). Premature infants have a higher incidence of refractive errors, including myopia, hyperopia, and astigmatism (Kaya, Berk, & Yaman, 2017; Zhu et al., 2017). Premature infants also have anisometropia more commonly than term infants (Stewart, Hernandez, & Duncan, 2017). Many of these eye disorders are corrected with eye glasses.

Measurements. During an eye examination, it can be difficult to assess whether an eye is larger or smaller than normal. Therefore, certain measurements can be taken and compared with published data (Table 17.2). These measurements can be obtained during an eye examination. The interpupillary distance and the width of the palpebral fissure can be determined and abnormal values can indicate an underlying syndrome, for example, the small eyes of FAS. The interpupillary distance determines whether the eyes are spaced correctly. Hypotelorism and hypertelorism are abnormalities where the eyes are either too close together or widely spaced. The palpebral fissure is the eye opening and can be determined if the opening appears smaller than normal.

Retinal Examination. Although routine retinal examinations on all normal newborns are not indicated, a retinal examination or ophthalmology consult is indicated for the premature infant at risk for ROP or if physical examination findings suggest serious problems, such as cataracts or glaucoma. In addition, a retinal examination can be done with an ophthalmoscope and pupil dilation if needed to rule out abuse or trauma in older infants. About 26% to 32% of newborns born by spontaneous vaginal deliveries will have retinal hemorrhages at birth, most often bilateral, between the optic discs and the macula (Laghmari et al., 2014; Watts et al., 2013). The risk of retinal hemorrhage is greater with vacuum-assisted delivery (about 43%) and instrument-assisted deliveries with vacuum (about 52%; Laghmari et al., 2014; Watts et al., 2013). The incidence of retinal hemorrhage is decreased with an uncomplicated cesarean section (about 21%; Laghmari et al., 2014; Watts et al., 2013). Most retinal hemorrhages from birth resolve within 1 to 2 weeks; however, resolution of retinal hemorrhages may be delayed if labor was induced or forceps used for the delivery (Laghmari et al., 2014). **Emergency Alert: Shaken baby syndrome would need to be part of the differential diagnosis of retinal hemorrhage seen after a month or longer of age.**

Eye Drops. Specific eye drops are used routinely for dilating the eyes in newborns who require a retinal examination. These medications, which are adrenergic agonists (phenylephrine) and cholinergic antagonists (cyclopentolate), can be absorbed into the newborn's systemic circulation. Complications from dilatation medications need to be observed for in the premature or term infant undergoing a retinal examination. These systemic effects are hypertension, tachycardia, arrhythmias, feeding intolerance, and skin rashes (de Alba Campomanes & Binenbaum, 2018). As a result, intracranial and intraventricular hemorrhage (IVH), necrotizing enterocolitis, and other major insults can occur, especially in a premature infant.

Quality and Safety: To decrease absorption by the infant, excess medication needs to be readily cleaned away from the skin to prevent systemic absorption. Also, applying pressure to the lacrimal sac for about 1 to 2 minutes after instillation may minimize reabsorption (de Alba Campomanes & Binenbaum, 2018).

After a retinal examination, the infant's eyes should be shielded from light or covered with eye shields until the pupils return to normal size. Dilated eyes exposed to bright lights may cause pain, distress, agitation, apnea, or bradycardia (Wood & Kaufman, 2009).

NEONATAL CONJUNCTIVITIS

Neonatal conjunctivitis or ophthalmia neonatorum ("pink eye") is an eye infection or inflammation of the conjunctiva or covering of the eyes causing redness, swelling, and discharge within the first 30 days of life. It can occur due to bacteria, virus, or other pathogen, often in the vaginal canal at birth. Aseptic conjunctivitis can occur because of a chemical reaction to eye medication administered after birth, which rarely occurs with erythromycin ointment. The incidence of septic neonatal conjunctivitis with either gonorrhea or chlamydia in the United States is low (about 1%–2%). Chlamydial infection has replaced gonorrhea as the most common cause of eye infection in the United States and many other countries

(Zloto et al., 2016). Gonorrhea remains the most serious type of conjunctivitis in the United States. Septic neonatal conjunctivitis usually manifests with a discharge that develops shortly after birth. Because the origins of newborn conjunctivitis can vary, it is important to determine the exact cause of the infection. In some cases of conjunctivitis, rapid treatment is important to prevent vision loss.

The presentation of neonatal conjunctivitis varies with the cause of the inflammation or infection. Some findings, such as purulent eye discharge and erythema and edema of the eyelids, are present in almost all cases. Transient tearing or watery discharge may be noticed early in the infection process.

Eye Prophylaxis

Most of the United States requires prophylaxis against newborn gonorrheal conjunctivitis. **Quality and Safety: Erythromycin ophthalmic ointment (0.5%) is the only CDC-recommended therapy for prophylaxis of ophthalmia neonatorum available in the United States** (Mabry-Hernandez & Oliverio-Hoffman, 2010). Silver nitrate was first used as a prophylactic agent against ophthalmia neonatorum caused by the bacteria *Neisseria gonorrhoeae* and other bacteria in 1881. One drop of 1% silver nitrate into the eyes of newborns prevented gonococcal infection, corneal scarring, and possible blindness. During the early 1900s, many state legislatures passed laws requiring physicians to treat all newborns with a silver nitrate solution. Although penicillins were discovered in the late 1940s, silver nitrate continued to be used as the main prophylactic agent until the mid-1990s. Silver nitrate was effective against *N. gonorrhoeae* and most bacteria; however, it was not effective against *Chlamydia* organisms. For this reason, erythromycin ointment is now used for routine prophylaxis in newborn eyes after birth. Erythromycin and tetracycline ointments are both effective against a variety of microorganisms, including chlamydia and gonorrhea, but must be inserted into the eye and must be done soon after birth to prevent gonorrhea from invading the eye (American Academy of Pediatrics [AAP], 2018; de Alba Campomanes & Binenbaum, 2018).

Chlamydial Conjunctivitis (Inclusion Conjunctivitis)

Chlamydia trachomatis is the most common cause of conjunctivitis in the newborn. The bacteria are transmitted from the infected mother to the infant at birth, and conjunctivitis may appear at about 5 to 7 days of life (de Alba Campomanes & Binenbaum, 2018). The condition may be mild or moderate, and with proper treatment it resolves within 6 weeks. Pneumonitis or a chlamydial pneumonia can occur with the conjunctivitis. Clinical symptoms of conjunctivitis include swelling of the eyelids and a mild mucopurulent discharge. Chronic infection can lead to more serious consequences, such as conjunctival scarring, adhesions of the eyelid, and deposits of connective tissue under the cornea.

Although the eye infection generally is not serious, a chlamydial pneumonitis can develop in some infected neonates. Systemic therapy with oral erythromycin for 3 weeks is often necessary to eradicate the organism from the respiratory tract.

Gonorrheal Conjunctivitis

Routine prophylaxis of newborns has greatly reduced the incidence of gonorrheal conjunctivitis. Because of the potential for blindness from this infection, early detection and prompt treatment are critical. Gonorrheal conjunctivitis typically manifests as an acute, purulent, bilateral conjunctivitis with eyelid edema. **Quality and Safety: If not treated appropriately and quickly, the infection may progress to corneal ulceration, endophthalmitis, and perforation of the globe** (de Alba Campomanes & Binenbaum, 2018). Gram stains and cultures should be performed routinely in all cases of neonatal conjunctivitis. The presence of *N. gonorrhoeae* confirms the diagnosis. Treatment consists of administration of intravenous or intramuscular antibiotics and application of topical antibiotics to the eye.

Staphylococcal Conjunctivitis

Staphylococcal conjunctivitis is a bacterial infection usually acquired during vaginal delivery or by contact with an infected individual. Symptoms normally appear about 2 to 4 weeks after birth. In most cases, the conjunctivitis is mild and produces a purulent discharge. It may progress to corneal ulceration, endophthalmitis, or generalized skin infection. The diagnosis is made with cultures and Gram stain. Because staphylococci can be found in the conjunctiva of healthy neonates, laboratory results should be interpreted cautiously. Treatment includes application of topical antibiotic ointment and cleansing of exudate from the eyelids.

Herpes Simplex Conjunctivitis

Herpes simplex infection at birth may be a feature of either localized or systemic disease. The newborn usually is infected during passage through the birth canal. Infants with herpes conjunctivitis exhibit eyelid swelling, inflammation, and corneal opacification. The onset of the conjunctivitis usually occurs about 2 to 14 days after birth. The disseminated form of the disease may also lead to chorioretinitis, microphthalmia, cataracts, optic atrophy, apnea, respiratory distress, and death (James & Kimberlin, 2015). This disease should always be kept in mind when the mother or father has a history of genital herpes. Treatment should be instituted immediately upon diagnosis. Systemic treatment (intravenous) is necessary for infants whose conjunctivitis has spread to be a systemic infection.

Infectious Conjunctivitis Caused by Other Microorganisms

There have been some case reports describing neonatal infectious conjunctivitis caused by other more unusual microorganisms. This is a rare occurrence but has been seen with a term infant readmitted at 10 days of age with conjunctivitis caused by *Neisseria meningitidis*, a gram-negative meningococcal disease (Chacon-Cruz et al., 2017). These infants require local and systemic treatment. *Neisseria meningitidis* can cause a serious, systemic infection with significant morbidity and mortality, and needs to be considered with an ill infant with a purulent conjunctivitis.

Premature infants in the neonatal intensive care units (NICUs) frequently are colonized with *Pseudomonas aeruginosa* or a variety of *Candida* species. These infants often will develop a purulent mucus discharge from the eyes. The infants may also develop simultaneous systemic infections. Eye involvement usually is limited to chorioretinitis that resolves with systemic antifungal therapy. Very low birth weight infants are at risk for more serious and deadly complications of any infection. Conjunctivitis has also occurred in the preterm infant with coagulase-negative *Staphylococcus*, *Klebsiella pneumoniae*, *Escherichia coli*, methicillin-susceptible or -resistant *Staphylococcus aureus*, *Enterococcus* species, and with various types of viruses.

LACRIMAL DYSFUNCTION

Obstructed Nasolacrimal Duct

Blockage of the nasolacrimal duct occurs when the duct fails to canalize at the entrance to the nose, leaving a thin membrane. This blockage occurs in about 5% of all newborns and is a common

cause of chronic conjunctivitis in infants (de Alba Campomanes & Binenbaum, 2018). After a month of age, the infant shows excessive tearing and mucus discharge in the inner canthal region. Pressure on the lacrimal sac area usually causes pus or mucus to exude from the opening. Because the problem resolves spontaneously in most affected infants by 6 months of age, conservative treatment involving lacrimal massage and application of topical antibiotics is recommended. Dacryocystitis can occur as a result of this temporary obstruction. Dacryocystitis is a secondary infection of the lacrimal sac. Obstruction that lasts beyond 6 to 12 months may require lacrimal probing. Nasolacrimal duct blockage should be differentiated from other causes of conjunctivitis, a foreign body on the eye, or corneal injury.

Mucocele

Mucoceles occur because of the one-way valve effect at the end of the nasolacrimal duct. Mucus accumulates or amniotic fluid is trapped in the nasolacrimal sac, and the infant develops a bluish mass in the inferomedial region of the eyelid. This swelling most often is confused with a hemangioma. If simple massage does not decompress the mucocele, probing of the nasolacrimal duct may be necessary.

CONGENITAL DEFECTS

Aniridia

Aniridia is a severe ocular abnormality that manifests as a bilateral absence of the iris. Cataracts, corneal pannus (fine blood vessel growth on the cornea), macular dysfunction, and glaucoma usually accompany the defect. Most of these infants have significantly diminished visual acuity. Aniridia can be caused by a deletion of a part of chromosome 11. Some children with aniridia develop Wilms' tumor during childhood due to the Wilms tumor gene is close to the aniridia gene location and these defects can occur together (Örge & Grigorian, 2015).

Persistent Hyperplastic Primary Vitreous

Persistent hyperplastic primary vitreous is a unilateral disorder that affects both genders equally. It results from persistence of the hyaloid vessels that connect the optic nerve and the posterior surface of the lens during fetal development. It should be considered in the differential diagnosis of leukocoria. The involved eye is usually small with an absent red reflex. Surgery may improve the integrity of the eye, and useful vision is sometimes restored.

Capillary Hemangioma of the Eyelid

Capillary hemangiomas are relatively common in newborns and tend to occur on the eyelids and nape of the neck. They are sometimes referred to as salmon patches or stork bites. They usually disappear over time and require no treatment. The larger and deeper strawberry hemangiomas tend to enlarge, stabilize, and then regress by the time the child is between 5 and 10 years old. These hemangiomas are usually elevated and reddish purple at their peak size. There are also larger and deeper hemangiomas called cavernous hemangiomas, which usually grow under the skin. No treatment is usually necessary, but it would depend on the location of the growth. Superficial tumors of the eyelid may cause cosmetic and visual problems. Parents often are concerned with hemangiomas on the face and want them removed, but no treatment is the best option to prevent scarring. Pressure on the eye from the tumor may result in significant astigmatism and subsequently amblyopia. Hemangiomas may be treated with surgical removal, radiation, or steroid injections. Tumors that are exclusively cosmetic should be allowed to regress without intervention.

Another type of hemangioma is called the port-wine stain, because of its dark purple pigmentation and location on the face. It is also called nevus flammeus and is associated with Sturge–Weber syndrome. These birth marks are extensive and usually removed with laser therapy.

Ptosis

Ptosis is a drooping of one or both eyelids due to neurologic, muscular, or mechanical factors. If the ptosis is significant enough to cover the pupil, amblyopia may result. If bilateral ptosis is present, the infant may have slowed motor development and delayed ambulation later in life. Congenital ptosis is usually caused by an abnormality in the development of the levator palpebrae muscle, but other causes can be third nerve palsy, Horner's syndrome, and blepharophimosis syndrome (de Alba Campomanes & Binenbaum, 2018). A thorough family history should be obtained as well as ruling out birth trauma to the cervical ganglion. Direct trauma to the eyelid or a tumor in the eyelid may also cause ptosis. Surgical repair corrects this defect.

Congenital Glaucoma

Primary congenital glaucoma occurs when there is a rise in the intraocular pressure causing enlargement of the eye with a cloudy cornea. This increased pressure results in damage to the optic nerve. Glaucoma is rare in newborns but because of the potential for blindness, glaucoma must be detected early and treated. The newborn shows tearing, light sensitivity, eyelid spasm, and a large, cloudy cornea. The diagnosis is often missed until the child is about 2 to 3 months of age. Conditions associated with glaucoma include trisomy 21, congenital rubella, Marfan syndrome, neurofibromatosis, oculodentodigital syndrome, Rieger's syndrome, Sturge–Weber syndrome, Rubinstein–Taybi syndrome, and Weill–Marchesani syndrome (Örge & Grigorian, 2015).

Emergency Alert: It is critical that congenital glaucoma be differentiated from other diseases that have similar symptoms. Nasolacrimal duct obstruction involves tearing but does not cause light sensitivity or a cloudy cornea. Difficult labor or forceps injury may damage the cornea and cause temporary clouding, but the intraocular pressure is not elevated, a hallmark feature of glaucoma. The large eyes of the infant with congenital glaucoma may appear beautiful to the parents, but health professionals should be alert to the possibility of this disease.

The abnormality in congenital glaucoma is a deformity of the filtering system that controls the level of intraocular pressure in the eye. Congenital glaucoma is treated surgically. The results usually are good, but parents must be educated about the need for continued monitoring of this condition throughout the child's life.

Congenital Cataracts

The causes of significant lens opacity in the newborn are numerous. Cataracts are an important cause of blindness because they may interfere with the process of visual development early in the infant's life. For this reason, visually significant cataracts must be detected and treated before they cause amblyopia, which may be unresponsive to the most persistent treatment.

Heredity is an important cause of congenital cataracts. A thorough family history is critical in determining the cause of the lens opacity. The inheritance pattern may be autosomal dominant, autosomal recessive, or sex linked. A maternal history of diabetes, x-ray exposure, or malnutrition may be an important factor in cataract formation. In premature infants, transient cataracts or insignificant opacities are commonly seen as a result of

remnants of developmental tissues. ROP can also lead to cataracts in premature infants. Several inborn errors of metabolism cause cataracts, including galactosemia, Alport syndrome, Fabry disease, and Lowe syndrome. Intrauterine rubella infection is also associated with cataracts in the neonate.

Cataract surgery early in life is critical to the infant's visual rehabilitation. Useful vision is especially difficult to achieve in eyes with monocular cataracts. It is important for nurses to work closely with the infant's parents. The parents' persistence in handling contact lenses and in amblyopia therapy often determines the outcome for their child's vision.

Retinoblastoma

Retinoblastoma is a rare disorder, but also the most common eye neoplasm in childhood. Most tumors occur sporadically without a family history of the disease in approximately 1 in 14,000 to 18,000 live births in the United States (de Alba Campomanes & Bininbaum, 2018). Most retinoblastomas occur unilaterally with only about 25% bilateral, and most children are diagnosed before their second birthday (de Alba Campomanes & Bininbaum, 2018).

Quality and Safety: The most common presenting symptom is leukocoria. The tumor is highly malignant and may spread to the bone marrow, central nervous system (CNS), or other organs. Untreated patients rarely survive. The standard treatment for advanced cases of retinoblastoma is enucleation (removal of the eye). Less severe cases are treated with radiation, laser photocoagulation, or cryotherapy. Children with this tumor require close follow-up for possible recurrence after treatment. Parents must be educated about the disease so that they are aware of the need for constant monitoring of their child.

CONGENITAL INFECTIONS

Cytomegalovirus Infection

Most infants with congenital CMV will be asymptomatic. But in infants with symptomatic disease, ocular lesions may include chorioretinitis, optic nerve atrophy, strabismus, cataract, macular scarring, and visual impairment or blindness. Many infants with symptomatic CMV disease will have moderate to severe visual impairment (Khahaeni, 2017). Parents should be advised to seek routine eye screenings during childhood and later in life.

Rubella

Congenital rubella or German measles has virtually been eliminated in the United States due to its vaccination program, but the virus can still be found in other parts of the world; therefore, with international travel and parents withholding vaccinations, rubella may return. The rubella virus is responsible for many eye complications including cataracts, glaucoma, and microphthalmia, often together. The majority of newborns with congenital rubella have hearing, eye, and cardiac defects. Parents of a child with congenital rubella need to understand that vision problems may occur at any time and their child must be screened regularly.

Herpes Simplex Virus

Herpes simplex virus causes a wide variety of eye disorders in newborns. Though skin vesicles are the main sign of a herpes virus infection in the newborn, eye damage and CNS manifestations can also occur (Purewal et al., 2016). Other eye conditions that can be seen with a herpes virus infection are conjunctivitis, chorioretinitis, and cataracts (de Alba Campomanes & Binenbaum, 2018).

Varicella

Although rare, congenital infection caused by varicella, commonly known as chickenpox, produces eye anomalies in more than half of affected infants. These defects include microphthalmia, chorioretinitis, cataract, optic nerve atrophy, nystagmus, and anisocoria (unequal pupils; Mandelbrot, 2012).

Toxoplasmosis

Toxoplasma gondii is a parasitic organism with an affinity for brain and eye tissue. As with many other congenital infections, ocular anomalies vary depending on fetal age at the time of infection. The most common clinical presentation is chorioretinitis (often bilateral). Chorioretinitis is part of the classic triad of congenital toxoplasmosis with hydrocephalus and intracranial calcifications. Other ocular manifestations that can occur in the newborn are microphthalmia, strabismus, retinal detachment, and blindness (McAuley, 2014).

Lymphocytic Choriomeningitis Virus

Another viral infection, lymphocytic choriomeningitis virus (LCV), can also cause ocular defects. LCV is a single-strand RNA virus found in rodents, including house mice and hamsters. Outbreaks of LCV infection associated with mice tend to occur in trailer parks, inner-city dwellings, and substandard housing. The virus probably is transmitted by airborne droplets and by food contaminated by rodent urine or feces. It may also be transmitted by the bite of an infected animal (Kinori, Schwartzstein, Zeid, Kurup, & Mets, 2018).

Congenital LCV results in many ocular findings, including generalized chorioretinitis leading to scarring, optic nerve atrophy, nystagmus, and strabismus. Eye abnormalities may be the first or only manifestation noted initially with this viral infection (Kinori et al., 2018). Newborns with congenital infection are at significant risk for neurologic damage and death.

RETINOPATHY OF PREMATURITY

ROP, a disease arising from proliferation of abnormal blood vessels in the newborn retina, was first reported by Terry in 1942. His description of a fibrous growth behind the lens and retinal detachment in premature infants gave birth to the name retrolental fibroplasia (RLF). The name was changed to ROP in 1984 by an international committee charged with providing a uniform classification system for the disease. The original classification system, International Classification of Retinopathy of Prematurity (ICROP), used a standard description of the location of retinopathy (using zones and clock hours), the severity of the disease (stage), the presence of special risk factors (plus disease), and the features of regression (International Committee for the Classification of Retinopathy of Prematurity, 2005; Figure 17.2 for zone diagram).

In 2005, the International Committee for the Classification of ROP published updates to the original ICROP. Three changes to the ICROP were introduced: (a) recognition of a more virulent form of ROP, aggressive posterior ROP (AP-ROP); (b) an intermediate grade of plus disease (pre-plus) that occurs between normal posterior pole vessels and frank plus disease; and (c) a clinical tool for estimating the extent of zone I involvement.

AP-ROP is defined as a rapid, progressive form of ROP that quickly progresses to stage 5 ROP if left untreated. Characteristics of AP-ROP include posterior location and prominence of plus disease, usually in zone I, but may be in posterior zone II. Because of the aggressive nature of this disease, the diagnosis of AP-ROP is

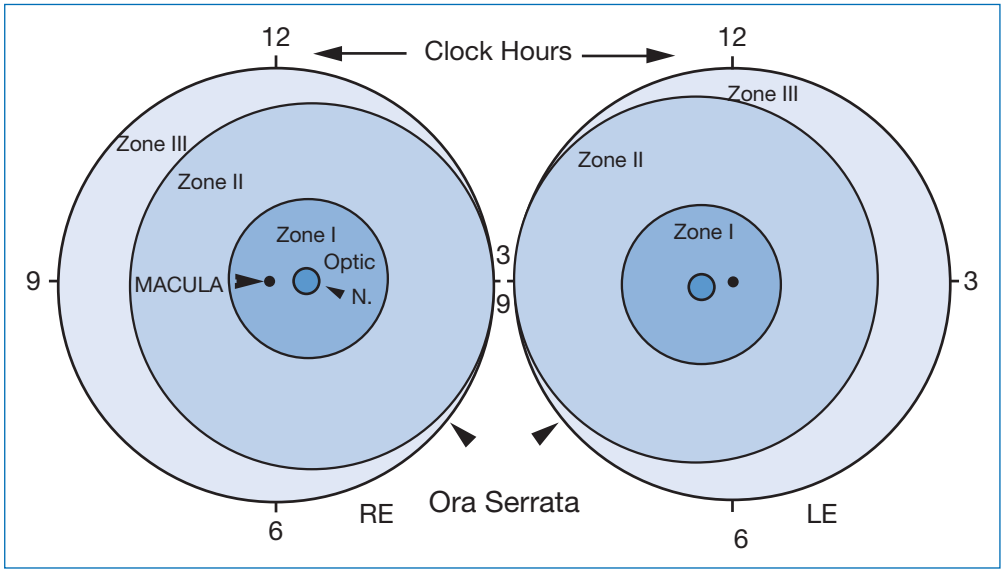

FIGURE 17.2 Diagram of zones of the eyes.

normally made during a single examination. The diagnosis of plus disease was modified from the presence of vascular dilatation and tortuosity in two to four quadrants. The new recommendations also included adding the + symbol after the ROP stage number to designate the presence of plus disease (e.g., stage 3+). The new term of pre-plus disease was defined as vascular abnormalities of the posterior pole that are insufficient for the diagnosis of plus disease but that demonstrate more arterial tortuosity and more venous dilatation than normal.

The 1986 multicenter CRYO-ROP trial led to the definition of threshold and prethreshold ROP. Threshold disease was considered the minimum disease needed for treatment. The 2000 to 2002 multicenter ET-ROP trial results substituted type 1 and type 2 as the equivalent but newly defined intervention and pre-intervention point. Type 1 is defined as zone I, any stage ROP with plus disease; zone I, stage 3 ROP without plus disease; or zone II, stage 2 or 3 with plus disease. Type 2 ROP is defined as zone I, stage 1 or 2 ROP without plus disease; or zone II, stage 3 ROP without plus disease (Reynolds, 2010).

ROP was responsible for an epidemic of blindness in young children in the 1940s and early 1950s until the link to supplemental oxygen therapy was made in 1952. Subsequently, the practice of limiting oxygen administration in the care of premature infants led to the near disappearance of the disorder; however, cerebral palsy and death increased. Improvements in neonatal healthcare in the past 35 years have increased the survival of tinier and sicker infants. As technology helped these smaller infants survive, the rate of ROP rose. The younger the gestational age and the lower the birth weight, the stronger the correlation with incidence of ROP (Drack, 2006). Results from the CRYO-ROP, LIGHT-ROP, and ET-ROP multicenter trials revealed that ROP occurs in 65% to 70% of premature infants with birth weights of 1,250 g or less (ET-ROP, 2003, 2005; Reynolds, 2010; Reynolds et al., 2002).

Pathophysiology

ROP is a disease caused by an abnormal adaptation of normal maturational processes in the face of physiologic stress. The disease develops gradually and is divided into five stages of increasing clinical severity (Table 17.3). Some ophthalmologists use the term stage 0 if the retina's vascularity is immature.

The key factor in the development of ROP, especially in premature infants, is the developing retinal blood vessels. The pathophysiology of ROP occurs in two phases. Phase I is delayed growth of the retinal vascularity following preterm birth. Phase II occurs when the hypoxia created during phase I stimulates the growth of new blood vessels (Smith, 2003). Retinal vascularization begins at the optic nerve at about 16 weeks' gestation. Retinal vascular development proceeds slowly and reaches the retinal periphery (ora serrata retinae) during the ninth month of gestation (Chen & Smith, 2007). The incompletely vascularized retina has a peripheral avascular zone that varies with the degree of immaturity of the retina (Smith, 2003). The in utero growth of retinal blood vessels is stimulated by the release of vascular endothelial growth factor (VEGF) and insulin-like growth factor-1 (IGF-1). VEGF is found at the front line of the growing retinal blood vessels, whereas IGF-1 is maintained at a constant level in the retina microenvironment. VEGF is a cytokine regulated by the amount of oxygen (hypoxia). IGF-1 is a nonoxygen-regulated cytokine involved in the regulation of endothelial cell survival and proliferation (Smith, 2004).

Following preterm birth, the normal growth of the retina vascularity stops and some of the already developed vessels are lost. The retina, however, remains metabolically active and becomes hypoxic because of the lack of blood vessels. This hypoxia becomes a potent inducer of new vessel growth (neovascularization) by stimulating the expression of VEGF at 32 to 34 weeks postmenstrual age. As the new blood vessels proliferate, they tend to grow into the vitreous and cause bleeding and the formation of fibrous tissue (Smith, 2003).

Many preterm infants in the NICU receive supplemental oxygen to treat their respiratory distress. The hyperoxia caused by oxygen use suppresses VEGF and IGF-1, resulting in programmed cell death, or apoptosis, of vascular endothelial cells, which in turn causes hyperoxia-induced vaso-obliteration and scarring of the retinal vessels (Smith, 2004).

As the preterm infant matures, the growing retina triggers a release of VEGF; IGF-1 levels will also rise. This creates an environment for new vessel growth (neovascular proliferation) that leads to the progression of retinopathy (Smith, 2003). Milder degrees of ROP are often transient and regress once the abnormal stimuli are removed or corrected. Moderate retinopathy can lead to excessive fibrous tissue formation or scarring in the peripheral retina, which may lead to traction on the macula and reduced vision. In severe

TABLE 17.3

STAGES OF RETINOPATHY OF PREMATURITY WITH POSSIBLE OUTCOMES

Stage	Finding	Possible Outcome
1	Demarcation line at avascular retina	Complete resolution probable
2	Ridge with height and width	May resolve
3	Ridge with fibrosis extending into vitreous	May resolve; prevention of detachment needed if plus disease
4	Partial retinal detachment with or without macula/fovea area involved	Visual impairment
5	Complete retinal detachment	Visual impairment/blindness
Pre-plus disease	Some increased tortuosity of retinal vessels	May resolve
Plus disease	Increased dilation and tortuosity of retinal vessels in two or more quadrants	Increased risk of impaired vision
Type 1 ROP	Zone I = any stage ROP with plus disease or stage 3 ROP without plus disease Zone II = stage 2 or 3 ROP with plus	Higher risk of impaired vision
Type 2 ROP	Zone I = stage 1 or 2 ROP without plus Zone II = stage 3 ROP without plus	Lower risk of impaired vision

ROP, retinopathy of prematurity.

Sources: Adapted from: Fleck, B. W., & McIntosh, N. (2009). Retinopathy of prematurity: Recent developments. *NeoReviews, 10*(1), e20–e30. doi:10.1542/neo.10-1-e20; and Jefferies, A. L. (2016). Retinopathy of prematurity: An update on screening and management. *Paediatric Child Health, 21*(2), 101–104. doi:10.1093/pch/21.2.101

cases of ROP, fibrous tissue development may lead to retinal detachment and blindness. Severely affected neonates may also have leukocoria, glaucoma, or both.

Risk Factors

ROP is a multifactorial disease that occurs primarily in premature infants. Although many risk factors have been identified, prematurity and low birth weight remain the most important factors leading to the development of ROP (Allegaert, deCoen, Devilieger, & EpiBel Study Group, 2004; Reynolds, 2010). The incidence of ROP strongly correlates with birth weight and gestational age at birth. ROP is twice as common in infants born at less than 750 g than infants born between 1,000 and 1,250 g (Reynolds, 2010). Even more dramatic, these two groups have a sevenfold difference in the incidence of threshold ROP.

Other epidemiologic facts include a higher risk of ROP in White infants than Black infants, infants born at outlying hospitals that require transport to a Level III NICU, and infants of multiple births (Reynolds, 2010). Other risk factors are associated with the management of the extremely preterm infant: supplemental oxygen, fluctuating oxygen saturations, continuous positive pressure ventilation, IVH, acidosis, blood transfusions, maternal preeclampsia, and intrauterine growth restriction (IUGR; Allegaert et al., 2004; Anderson, Benitz, & Madan, 2004; Darlow et al., 2005; Reynolds, 2010; York, Landers, Kirby, Arbogast, & Penn, 2004).

According to Chow, Wright, Sola, and the CSMC Oxygen Administration Study Group (2003), the rate of severe, stage 3 and 4 ROP was reduced from 38% to 12% in infants with a birth weight less than 750 g by strictly maintaining oxygen saturations between 85% and 95% (and between 83% and 93% on the smallest infants). The studies that keep oxygen saturations in the low 90% level can reduce the rate of severe ROP significantly (Drack, 2006). Recently, the BOOST II Collaborative Group (2013) published data showing a lower mortality rate in infants less than 28 weeks who were kept in lower oxygen (with saturations <90%) compared with infants whose saturations remained higher than 90%. Their study shows that even though the rates of ROP can be lowered with lowered oxygen saturations, the higher risk of death in these tiny infants must also be considered. Therefore, many NICUs are now keeping oxygen saturation levels of the extremely premature infants in the low 90s.

Other factors such as breast milk feedings and the use of nitric oxide in the treatment of respiratory distress in preterm infants may provide some protection against the development of ROP. Hylander, Strobino, Pessullo, and Dhanireddy (2001) found that preterm infants weighing less than 1,500 g at birth who received human milk feedings had a lower incidence of ROP when compared with preterm infants who were formula fed. The positive benefit of human milk feeding remained after adjusting for confounding variables such as birth weight, race, and duration of oxygen therapy. Mestan, Marks, Hecox, Huo, and Schreiber (2005) reported that treatment with nitric oxide improved the neurodevelopmental outcomes of preterm infants at 2 years of age. The incidence of severe ROP was 24% in the nitric oxide group and 46% in the placebo group of preterm infants.

Although most ROP occurs in premature infants, rare cases of the disease have been reported in full-term infants, stillborn infants, and infants who have not received supplemental oxygen. In several studies, variations in the Norrie disease gene, a gene responsible for an X-linked form of congenital retinal detachment or dysgenesis, were more common in infants with severe ROP than in those in whom the disease resolved on its own. Each individual carries genetic predispositions to certain disorders, but less understood are the genetic proclivities toward outside effects—trauma, hypoxia, and premature birth among them (Drack, 2006). Further research is needed to increase our understanding of the cause and the pathophysiology of this disease.

Treatment

Treatment of ROP can be divided into three categories: preventive, interdictive, and corrective. Until premature birth can be eradicated, the major focus of ROP treatment is early detection and appropriate follow-up of significant disease. Despite the international effort to standardize ROP and the efforts of the several multicenter, randomized clinical trials, no universally accepted guidelines exist for the screening of premature infants. Screening protocols vary from institution to institution, among different countries, and even with the level of development of the countries (Table 17.4; Fierson & AAP, 2018; Jefferies, 2016; Royal College of Ophthalmologists, 2008).

According to Roth et al. (2001), indirect ophthalmoscopy by an experienced ophthalmologist in the NICU has traditionally been considered the standard method for detection of ROP. These examinations can be physiologically stressful for the infants, time consuming for the ophthalmologist, and costly for the medical system. A mydriatic agent (e.g., phenylephrine 2.5%, cyclopentolate 0.5%, or tropicamide 0.5%) is instilled topically for pupil dilation approximately 30 to 45 minutes prior to the examination. A topical anesthetic, such as 0.5% proparacaine HCl ophthalmic solution, should be instilled in each eye, to dull the corneal and conjunctival sensitivity and decrease the newborn's pain before the examination. A lid speculum and a sclera depressor, individually sterilized for each infant's examination, is used to visualize the peripheral retina and ora serrata, the anterior border of retinal vascularization, or retinopathy (Figure 17.3). Examinations are performed with the binocular indirect ophthalmoscope and 30-diopter lens, first evaluating the posterior pole and then the periphery with sclera depression. The presence or absence of ROP disease, its location and extent, and the presence or absence of plus disease are documented at the time of examination according to the international classification of ROP.

A wide-field digital camera (RetCam) is being used as an alternative to indirect ophthalmoscopy for screening infants for ROP. Retinal images taken by the camera can be stored, transmitted to an expert, reviewed, analyzed and sequentially compared

TABLE 17.4

RETINOPATHY OF PREMATURITY SCREENING GUIDELINES

Recommending Group	Infant Criteria	First Examination Date	
American Academy of Pediatrics American Academy of Ophthalmology American Association of Pediatric Ophthalmology and Strabismus	• Birthweight <1,500 g or gestational age ≤30 weeks • Selected infants between 1,500 and 2,000 g with an unstable clinical course	*GA @ birth*	*Age at initial examination*
		22 weeks	9 weeks
		23 weeks	8 weeks
		24 weeks	7 weeks
		25 weeks	6 weeks
		26 weeks	5 weeks
		27–32 weeks	4 weeks
Canadian Pediatric Society Canadian Association of Pediatric Ophthalmologists	• Birthweight ≤1,250 g OR • Gestational age ≤30 6/7 weeks	• ≤26 6/7 weeks @ birth, age at initial examination should be @ 31 weeks PMA • ≥27 weeks @ birth, infant should be 4 weeks chronologic age	
Royal College of Ophthalmologists	• Birthweight <1,501 g or <32 weeks at birth SHOULD be screened • Birthweight <1,251 g or <31 weeks at birth MUST be screened	• <27 weeks @ birth, initial examination should be @ 30–31 weeks PMA • 27–32 weeks @ birth, initial examination should be @ 4–5 weeks chronologic age • >32 weeks @ birth, but with birth weight <1,501 g, initial examination should be @ 4–5 weeks chronologic age	

ROP, retinopathy of prematurity.

Sources: Adapted from Fierson, W. M., & American Academy of Pediatrics Section on Ophthalmology, American Academy of Ophthalmology, American Association for Pediatric Ophthalmology & Strabismus, American Association of Certified Orthoptists. (2018). Screening examination of premature infants for retinopathy of prematurity. *Pediatrics, 142*(6), e20183061.

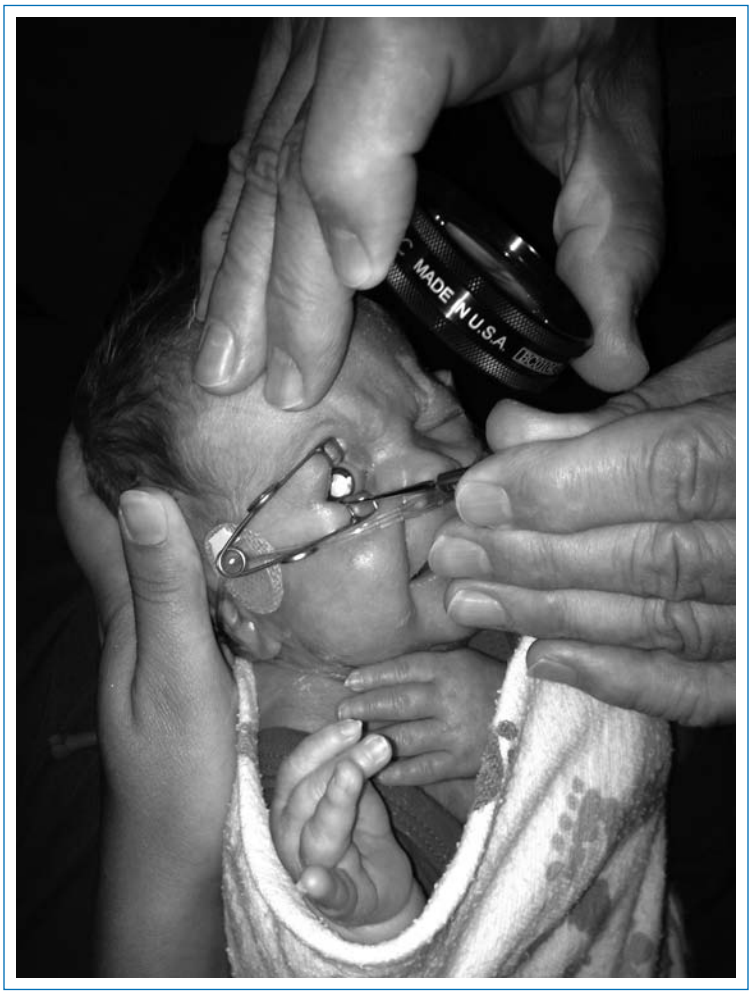

FIGURE 17.3 Premature infant during eye examination undergoing indirect ophthalmoscopy using eyelid speculum and sclera depressor.

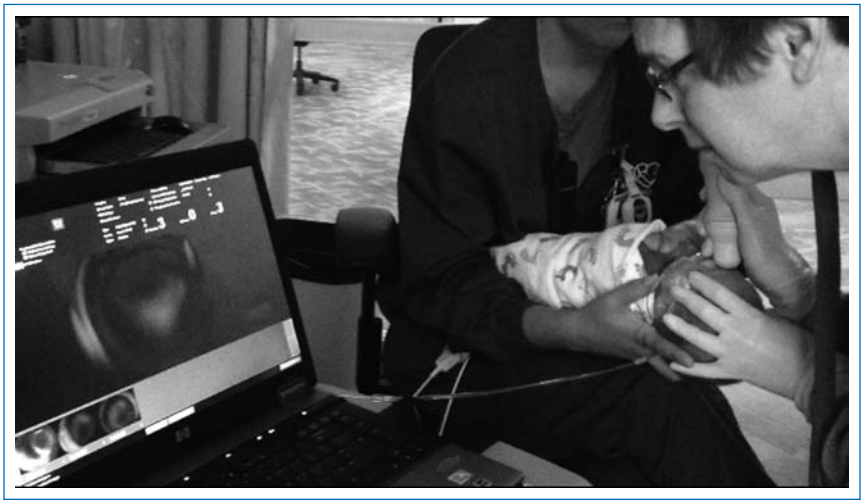

FIGURE 17.4 Premature infant during retinal evaluation using the RetCam.

over time, and are useful for telemedicine purposes (Chawla et al., 2012). The same eye drops must be utilized to dilate the pupils and anesthetize the area. The eyelid speculum is also used, but the scleral depressor is not needed. A water-soluble gel is applied to serve as a barrier between the eye and the lens.

Timing for eye examinations can be frustrating for not only the NICU staff, but also for the ophthalmologist. Often, the ophthalmologist may arrive to examine an infant when the infant is due to eat, or the infant has just completed his feed, or during the infant's scheduled "quiet time." Use of the RetCam allows examinations to be scheduled at the convenience of the NICU staff, are less traumatic to the infant, and provide for permanent documentation through the digital images (Roth et al., 2001; Figure 17.4).

Oxygen monitoring has been the major emphasis in the prevention of ROP. Elaborate policies and practices for continuous monitoring of oxygenation have evolved over the years, including evasive methods (fiberoptic umbilical catheters) and noninvasive techniques (transcutaneous oxygen monitoring, and pulse oximetry). Despite these efforts, little data indicate a safe level of oxygenation in premature infants at risk for ROP (Saugstad, 2005). Early efforts at restricting oxygen delivery in the 1950s and 1960s traded visual problems for neurologic sequelae. Recent practice changes are aimed at minimizing oxygen exposure while preserving optimum functioning of vital organs. Further research is being done to determine appropriate strategies.

Environmental lighting in NICUs has been implicated as a contributing factor in the development of ROP. Although some clinical studies claimed to show this relationship, they had many limitations. A large multicentered, randomized controlled trial (RCT) was completed and published in 1998, which showed that there was no statistically significant difference between the infants exposed to ambient lighting and those wearing light-reduction goggles during their first few weeks of life (Reynolds et al., 1998). Despite this evidence, many NICUs continue to institute reduced environmental lighting and shielding of incubators as part of a developmental approach to care.

The second strategy for treating ROP focuses on therapies aimed at minimizing or preventing blindness once the disease has developed. Interdictive therapies include cryotherapy, laser photocoagulation, and/or treatment with anti-VEGF drugs (Shah et al., 2016).

Cryotherapy was developed in Japan in the 1970s. It gained popularity in the United States in the 1980s after the release of data from the Cryotherapy for ROP Study. Cryotherapy is a surgical procedure involving insertion of a probe cooled with liquid nitrogen on the medial aspect of the eye. Confluent spots on the avascular retina are ablated (destroyed by freezing), reducing the release of angiogenic factors that appear to induce retinal vasoproliferation.

Transpupillary laser photocoagulation delivered through an indirect ophthalmoscope has essentially replaced cryotherapy as the treatment of choice for ROP (Coats & Reddy, 2009). Argon and infrared diode lasers are used to ablate the avascular retina in a manner similar to that used in cryotherapy. Advantages of the laser photocoagulation therapy include the technical ease of performance and its usefulness in posterior ROP that was difficult to treat with cryotherapy, and requires less eye manipulation. In addition, it is less traumatic for the patient, and there are fewer delayed consequences of myopia and retinal detachment. Using cost-utility analysis, healthcare economists have determined that laser ablation surgery for threshold ROP is cost effective (M. M. Brown & Brown, 2005; M. M. Brown, Brown, & Sharma, 2004).

Treatment can be performed in either the operating room or within the NICU. Sedation and either retrobulbar anesthesia or general anesthesia can be utilized, dependent on the preferences of the ophthalmologist and anesthesiologist, and the medical condition of the infant. Major potential complications of laser treatment include diminished peripheral vision, intraocular bleeding, cataract formation, myopia, and retinal detachment (Coats & Reddy, 2009). A known side effect of laser ablation therapy is angle-closure glaucoma in infants with severe ROP (Trigler, Weaver, O'Neil, Barondes, & Freedman, 2005).

Results of multicenter clinical trials suggest that earlier treatment of ROP is more important than the type of treatment. The Early Treatment for ROP (ET-ROP) clinical trial found that unfavorable outcomes at the 9-month follow-up appointment were significantly reduced in the early treatment of eyes (ET-ROP Cooperative Group, 2003). Both cryotherapy and laser photocoagulation were used in the clinical trial, and the study group recommended retinal ablation therapy "for any eye with type 1 ROP" and serial examinations for those with type 2 ROP. In another study comparing early versus conventional treatment of prethreshold disease, no significant differences were noted in the prevalence of myopia (Davitt et al., 2005). Thus, it appears that early treatment of ROP is beneficial to the infant.

Research with anti-VEGF drugs has revealed a new treatment for ROP that is showing promising results. The U.S. Food and Drug Administration (FDA) approved the use of bevacizumab for the treatment of metastatic colorectal cancer in 2004. The drug was shown to reduce the size and number of new vessels feeding the area of metastasis. Off-label use of bevacizumab for the treatment of neovascular ophthalmologic diseases began shortly thereafter (Hård & Hellström, 2011).

According to Mintz-Hittner, Kennedy, Chuang, and BEAT-ROP Cooperative Group (2011), bevacizumab (Avastin) is relatively inexpensive and is available for recommended use in infants with zone I posterior stage 3+ disease. Administration of the drug decreases the high levels of VEGF in the vitreous gel, which are not reduced by conventional laser therapy. Development of peripheral retinal vessels continues after treatment with intravitreal bevacizumab, whereas conventional laser therapy leads to the permanent destruction of the peripheral retina. Compared to laser ablation surgery, where the infant requires intubation and where there is known peripheral field loss and possibly myopia, the use of bevacizumab is relatively benign; anesthesia is achieved through topical drops. The drug is administered intravitreally. Using a tiny needle. Ocular inflammation has been observed after seven or more injections of the drug.

There are other FDA-approved drugs for eye injections, such as ranibizumab (Lucentis), aflibercept (Eylea), and pegaptanib (Macugen), also are being studied and used as ROP treatments. Intravitreal bevacizumab reduces the risk of refractive errors during childhood when used as monotherapy while intravitreal pegaptanib reduces the risk of retinal detachment when used in conjunction with laser therapy in infants with type 1 ROP. However, the long-term systemic adverse effects of these drugs are not known (Sankar, Sankar, Mehta, Bhat, & Srinivasan, 2016).

VEGF plays many positive roles in neural, vascular, and lung development. Bevacizumab has been shown to leak into the systemic circulation, suppressing systemic VEGF at least 8 weeks after injection, which may cause changes in brain and other organ development in very preterm infants (Shah et al., 2016). There are also concerns for recurrence of ROP after bevacizumab injection much later when compared with conventional laser peripheral retinal ablative therapy (16 ± 4.6 vs. 6.2 ± 5.7 weeks), requiring longer follow-up to ensure ROP requiring treatment does not recur (Mintz-Hittner et al., 2011).

According to the CARE-ROP study, ranibizumab was identified as an effective anti-VEGF alternative to bevacizumab. In comparison, ranibizumab has been shown to not suppress systemic VEGF levels, thus limiting unwanted effects on organs, like brain and lung, that are still undergoing development at the time of ROP treatment (Stahl et al., 2018).

Systemic propranolol, IGF-1 replacement, granulocyte colony-stimulating factor, Jun kinase inhibitor, and omega-3 polyunsaturated fatty acid supplementation are the newer preventive strategies being evaluated through insights into the molecular pathogenesis of ROP in animal studies. Newer emerging therapeutic options have the potential to complement current therapies and improve treatment outcomes (Shah et al., 2016). Continued research is necessary before changes in current modalities occur.

The focus of corrective treatment is surgery for the repair of the detached retina. Scleral buckling, vitrectomy, or both, with or without lensectomy, are the techniques most often used. Scleral buckling involves the placement of a silicone or plastic band

around the globe of the eye. The band is tightened, which brings the sclera closer to the retina, facilitating retinal reattachment. This procedure is often performed in conjunction with laser therapy to salvage any remaining vision (Ertzbischoff, 2004).

When retinal detachment progresses beyond the point of scleral buckling, the ophthalmologist must consider anatomic reattachment of the retina. Vitrectomy involves surgically opening the eye, removing the lens, and gently excising the proliferative scar tissue; this allows the retina to lie against the pigmented epithelium and hopefully reattach. Despite the skill required for these procedures, most infants who undergo corrective therapy do not experience significant improvement in their vision. The best surgical reattachment rates (>50%) occurred when the surgery was performed on infants between 2 and 9 months of age. In addition, the level of visual function did not correlate with the degree of retinal reattachment. Poor visual outcomes have occurred regardless of the timeliness or delay in surgical reattachment (Ertzbischoff, 2004).

Outcome studies suggest that the incidence of long-term problems associated with ROP has been underestimated. Although studies on the natural history of ROP in the postsurfactant era consistently support an increased rate of mild ROP, which usually regresses, the consequences of severe ROP, especially stage 3 or greater, disease remain less than desirable. At 18 months of age, 34.5% of preterm infants with threshold ROP had complications consisting of strabismus, nystagmus, myopia, and late retinal detachment (O'Connor, Vohr, Tucker, & Cashore, 2003). Fifteen percent of the infants were legally blind.

Prematurity without ROP is also associated with poor visual outcomes. According to Cooke, Foulder-Hughes, Newsham, and Clarke (2004), preterm infants are three times more likely to wear glasses, three to four times more likely to have poor visual acuity or stereopsis (3D vision or depth perception), and 10 times more likely to have strabismus. Poor school performance in this population of preterm infants was also attributed to visual impairments. Because none of the infants with poor visual outcomes had intraventricular hemorrhages (IVH) or periventricular leukomalacia (PVL), poor school performance could not be explained by neurologic problems. Larsson, Rydberg, and Holmstrom (2005) showed that preterm infants have decreased distance and near vision acuities when compared with full-term infants.

Collaborative Care

Health professionals have to be concerned about care of the individual infant with ROP and the families of those infants. A nursery nurse may be caring for a convalescing infant who is being transported back to a community hospital, or an infant who is discharged prior to the first ROP screening examination. Attar, Gates, Iatrow, Lang, and Bratton (2005) found that infants transported back to a community hospital often missed their follow-up eye examinations when compared with those discharged directly from the regional perinatal–neonatal unit. The same authors found that infants discharged prior to their first ROP examination were more likely to miss follow-up eye care than those infants who had their first examination while in the NICU. It is imperative that there is clear, concise communication to the receiving hospital and to the parents about the importance of initial and follow-up eye examinations.

The development of ROP is concerning to parents of premature infants. Open communication between the neonatal healthcare team and the parents is crucial for helping the parents successfully cope with the stress of a hospitalized premature infant. At first, general information about the relationship of ROP and prematurity can be shared with the parents. After the initial eye examination has been performed, the information can be specific to their baby. The neonatal healthcare team must work closely with the ophthalmologist to provide a consistent message to the family. Parent teaching should focus on providing a basic understanding of ROP, the purpose of the screening examinations, and the importance of regular vision testing for their infant after discharge. Misconceptions about the disease and the use of oxygen need to be corrected.

Once ROP is diagnosed in an infant, parents may need more support than usual. Some parents may exhibit denial because they cannot see any physical evidence of a problem. Families of infants who need surgical intervention may feel greater stress from their concern for their infant's vision and may need the added communication with an ophthalmologist or retinal surgeon. NICU staff members can help parents cope by providing support during decision-making sessions with the eye specialists, by asking questions to clarify information, and by reinforcing information provided. It is also important to determine if parents are obtaining information from outside sources on the Internet. An analysis of 114 Internet sources on ROP found that 62.5% of the sites evaluated contained poor to fair information (Martins & Morse, 2005). Of the websites analyzed, 25% were academic, 20% were organizational, and 55% were commercial.

Information given to the parents about the prognosis of ROP in their infant must be included in any discharge planning. Parents need to understand that eye problems are more common in premature infants and may develop in infants with regressed ROP. Myopia (nearsightedness), strabismus (crossed eye), astigmatism, and amblyopia (lazy eye) are common sequelae. Glaucoma and late retinal detachment are common sequelae in infants with severe ROP.

Clearly, early detection and referral to programs for visual impairment are essential. Parents need to understand the importance of regular eye examinations by a pediatric ophthalmologist or by an ophthalmologist knowledgeable about ROP and its complications. Many families may benefit from referral to community resources, support groups, and special programs for children with visual problems.

Lastly, the nursing staff and unit managers have to maintain vigilance about infection control practices during eye examinations, laser ablation surgery, or intravitreal injections that occur within the NICU. Major risk factors for nosocomial infection are unwashed or poorly washed hands, and the sterility of instruments such as eyelid speculums and eye probes.

OTHER DISORDERS THAT AFFECT THE EYES

Fetal Alcohol Spectrum Disorders

Maternal ingestion of alcohol during pregnancy results in fetal alcohol spectrum disorders (FASDs) including the most severe type, FAS. Infants with FAS have mental deficiencies (CNS damage), dysmorphic facies, and severe IUGR. The abnormalities of the eyes common in infants with FAS include microphthalmia, short palpebral fissures, hypertelorism, coloboma, strabismus, ptosis, and optic nerve hypoplasia (Nash & Davies, 2017). Most affected infants have diminished visual acuity and some infants can develop blindness (Burd, 2016; O'Neil, 2011).

Zika Virus

Zika virus is a mosquito-borne virus that was discovered in Uganda in the 1940s, but has now been found in South America, Central America, and even in the southern part of the United States. Adults bitten by a Zika-infected mosquito often develop only a mild version of the disease. Zika virus can also be transmitted to the fetus if the mother was infected with the virus during pregnancy. The fetus can develop brain damage and death depending on the extent of the exposure and infection.

Infants who are exposed to the Zika virus in utero can develop a number of congenital malformations. The most common

is microcephaly, but infants can also develop abnormal development of the eye, including inflammation of the optic nerve, lens subluxation, iris colobomas, damage to the retina (chorioretinal atrophy), macular atrophy, or even blindness. About one-third of infants develop some type of eye disorder (de Miranda et al., 2016; Jampol & Goldstein, 2016; Russo & Beltrao-Braga, 2017).

Maternal Diabetes

Although maternal diabetes is recognized for its teratogenic effects, craniofacial anomalies are rarely reported. Infants of diabetic mothers should be carefully examined for the presence of oculoauriculovertebral (OAV) complex of disorders, including displaced inner canthi, lens opacity, microphthalmia, optic nerve hypoplasia, tear duct obstruction, and ocular lipoma (Ewart-Toland et al., 2000). Wang, Martinez-Frias, and Graham (2002) suggested that OAV occurred as a result of faulty neural crest cell migration in diabetic women with poor control during pregnancy.

Periventricular Leukomalacia

PVL is a major cause of visual impairment in premature infants. Impairments found in infants with PVL included diminished visual acuity, eye movement disorders, and visual field restriction. Other eye problems included optic disc anomalies, nystagmus, strabismus, delayed visual maturation, and visual perceptual-cognitive problems (Jacobson & Dutton, 2000; Jacobson, Ygge, Flodmark, & Ek, 2002).

Intraventricular Hemorrhage

IVH without PVL is also associated with eye abnormalities. Visual impairments, including ROP, were common in infants with IVH, including strabismus, optical atrophy, small visual field, and poor acuity (O'Keefe, Kafil-Hussain, Flitcroft, & Lanigan, 2001). The increased cranial pressure on the developing eye and optic nerve with hydrocephalus-associated IVH can cause more visual acuity problems.

SUMMARY

Visual disturbances, although sometimes difficult to detect in newborns, can have a dramatic impact on a newborn's behavioral and psychosocial development. PVL and severe IVH with hydrocephalus can cause serious eye disease in premature infants. Significant advances are being made every day in the diagnosis, treatment, and follow-up of extremely low birth weight infants. Neuroprotective bundles and caffeine may improve long-term vision outcomes by decreasing the incidence of IVH and PVL (Chorna, Guzzetta, & Maitre, 2017). But visual morbidity continues to be a concern as these small neonates survive the NICU.

The treatment of vision problems requires collaborative efforts among the neonatal healthcare team, the ophthalmologist, and the families of affected children. Clear, consistent communication between healthcare providers and parents, parental education, and good follow-up are important to the quality of care.

CASE STUDY

■ **Identification of the Problem.** Premature infants, especially those weighing less than 1,500 g, are at risk for complications from immature development of the eyes and the effects of supplemental oxygen on the developing eyes. As a result of the supportive therapies used in the NICU, ROP can develop. This case study presents a patient born at 25 weeks' gestation who is presently 11 weeks of age or 36 weeks corrected gestational age. Due to his early birth, the infant has chronic lung disease (CLD), is on a mild diuretic, and continues to require a low amount of oxygen via nasal cannula. The plan is to discharge to home within 5 to 7 days.

■ **Assessment: History and Physical Examination.** Baby Boy TS was born on June 4, 2012, at 25 weeks' gestation to a 23-year-old, gravida 1, para 0 mother whose pregnancy was complicated by preterm labor. She received prenatal care and delivered spontaneously by vaginal route following 2 days of unsuccessful tocolysis treatment and rupture of membranes approximately 15 hours prior to birth. Baby Boy TS was born with minimal respiratory effort, requiring intubation, bagging, and surfactant treatment in the delivery room, but was extubated to nasal continuous positive airway pressure (CPAP). By 4 hours of age, he required moderate ventilation and his condition deteriorated, requiring high-frequency oscillatory ventilation by 24 hours of age. He received a second dose of surfactant and remained on ventilation for approximately 3 weeks. He was weaned to nasal CPAP, to high-flow oxygen, and then to low-flow oxygen. He remains on 200 to 250 mL/minute of oxygen via nasal cannula. He had umbilical lines placed after birth, peripherally-inserted central catheter (PICC) line for 12 days, started on nasogastric (NG) feedings that were well tolerated, and advanced to full feedings. He has been nippling feeds with occasional apnea and bradycardia.

■ **Physical Examination**

- GENERAL: preterm, male infant
- HEENT: slight dolichocephaly, anterior fontanel soft and flat with widened sagittal sutures; eyes clear, no drainage or redness; pupils reactive to light; positive red reflex OU; eyes and ears normoset with palate intact
- RESPIRATORY: lung fields clear and equal bilaterally; minimal respiratory effort; respiratory rate = 48 with saturations 89% to 93% on 200 mL/L nasal cannula oxygen
- CARDIOVASCULAR: regular rate and rhythm with no murmur; pulses strong, regular and equal in all extremities; good peripheral perfusion 2+/4+ and capillary blood refill time less than 3 seconds
- ABDOMEN: soft and nontender with no masses palpable and positive bowel sounds throughout; liver edge down 2 cm below right costal margin; no splenomegaly; patent anus
- GENITOURINARY: normal male genitalia with testes descended into scrotum bilaterally
- NEURO: awake and active; cries when distressed or disturbed; sleep pattern appropriate for near-term infant; normal tone and responsiveness for gestational age
- EXTREMITIES: moves all four extremities with normal range of motion; hips—no click; clavicles—no crepitus; good muscle tone of all extremities; 10 digits per extremity
- SKIN: pink, warm, dry, and intact; no rashes or bruising noted; mucous membranes pink and moist

Premature infants are at risk for many complications due to their immaturity and treatments.

■ **Premature Diagnoses**

- Respiratory distress syndrome—can develop into CLD
- Hypoglycemia
- At risk for patent ductus arteriosus
- Possible sepsis/pneumonia
- At risk for IVH
- At risk for ROP
- Apnea of prematurity
- Anemia of prematurity

■ ROP Examinations

Dates	Age (weeks)	Gestational Age (weeks)	Results	Plan
July 16, 2012	6	31	Immature vascularity in both eyes (stage 0, zones II–III bilaterally)	Follow-up in 2 weeks
July 30, 2012	8	33	Stage 1–2, zone II with questionable plus disease	Follow-up in 1 week
August 6, 2012	9	34	Stage 2–3+, zone II on right; stage 2+, zone II on left	Referral for laser treatment
August 8, 2012	9½	34½	Stage 3+, zone II bilaterally	Laser photocoagulation was performed

Note: According to the American Academy of Pediatrics (AAP), the first eye examination would be done at 6 weeks' gestation.

■ Discharge Diagnoses

- Premature male infant
- CLD
- Apnea of prematurity
- ROP

EVIDENCE-BASED PRACTICE BOX

In evaluating infants with ROP, neonatal researchers have conducted studies to assess the effects of supplemental oxygen provided to preterm infants in the NICU. There have been numerous studies on neonates with ROP or prevention of ROP (see Table 17.5). This table provides an in-depth look at studies between 1988 and 2010 on neonatal ROP prevention from around the world. The significant findings are listed within the table. On searching for meta-analyses of ROP studies, the Cochrane review (www.cochrane.org) has listed 20 literature summaries dealing with ROP in neonatal care. These summaries involve a variety of prevention methods, including uses of supplemental oxygen, early light reduction, retinal ablation therapy, and early versus late oxygen reduction.

On searching eye disorders, there are two literature summaries in neonatal care. There continue to be many studies on the prevention of eye disease and disorders, especially ROP. By searching Internet sites, nurses can find the newest evidence-based protocols for prevention of ROP and other eye disorders.

TABLE 17.5

ROP STUDIES

First Author	Location	Years Included	Gestational Age of Subjects	Birth Weight of Subjects	Type of Study	Significant Findings
Good (Chair)	US ET-ROP	2000–2002		<1,250 g	Prospective	Incidence of ROP 68% with more zone I and prethreshold disease than in the CRYO-ROP study of 1986–1987. Incidence unchanged by race; however, more prethreshold disease seen in White infants
Markestad	Sweden	1999–2000	22–27 weeks	500–999 g	Prospective, observational	33% of 23 weeks preterm infants needed ROP treatment compared with 0% >25 weeks

(*continued*)

TABLE 17.5

ROP STUDIES (*continued*)

First Author	Location	Years Included	Gestational Age of Subjects	Birth Weight of Subjects	Type of Study	Significant Findings
Chiang	US	1996–2000	All newborns hospitalized for >28 days		Population -based cohort	ROP incidence by BW: <600 g—32% 600–799 g—38% 800–999 g—30% 1,000–1,199 g—17% 1,200–1,499 g—8% 1,500–1,999 g—4% 2,000–2,499 g—2%
Hussain	US	1989–1997	22–36 weeks	600–1,832 g	Retrospective	All ROP—21% ≥Stage 3—5% >32 weeks—0%
Gilbert	International NO-ROP group	1996–2002	25.3–33.5 weeks	410–2,700 g	Observational	Mean GA/BW for severe ROP for: *Highly developed countries:* Canada 25.6/759 US 25.4/763 UK 25.3/737 *Moderately developed countries:* Argentina 30.2/1263 Brazil 27.7/952 Chile 26.8/903 Colombia 29.2/1,122 Cuba 30.7/1,285 Ecuador 33.5/1,259 Peru 29.1/1,051 *Poorly developed countries:* India 29.3/1,243 Vietnam 29.9/1,284
Lee	Canada	1996–1997	All admissions to Level 3 NICUs		Population -based cohort	Incidence of ROP: <1,500 g 43% >Stage 3 11%
Larsson	Sweden	1988–1990 1998–2000		<1,500 g	Prospective comparison to 1988–1990 data in same geographic region	Total ROP stayed the same (36.4% 2000 vs. 40% 1990) Change in distribution noted: *Incidence by GA:* ≤26 weeks—23% vs. 14% 27–29 weeks—42% vs. 48% 30–32 weeks—32% vs. 30% ≥33 weeks—4% vs. 9%

(*continued*)

TABLE 17.5

ROP STUDIES (*continued*)

First Author	Location	Years Included	Gestational Age of Subjects	Birth Weight of Subjects	Type of Study	Significant Findings
Larsson (*cont*)						*Incidence by BW:* ≤750 g—9% vs. 5% 751–1,000 g—27% vs. 24% >1,000 g—64% vs. 72%
Hameed	UK	1990–1994 1995–1999		≤1,250 g	Observational comparison in same geographic region	Survival—76% (1995–1999) Survival—62% (1990–1994) ≥Stage 3—12% (1995–1999) ≥Stage 3—4% (1990–1994)
O'Connor	US	1994–2000		≤1,250 g	Retrospective	Incidence of ROP increased from 2% to 5% Highest incidence and severity seen in BW <750 g
Fledelius	Denmark	1993–1997		<1,750 g	Retrospective	Incidence of ROP—10%
Mintz-Hittner	US multicenter BEAT-ROP		<30 weeks	<1,500 g	Prospective, randomized, controlled	Increased efficacy of intravitreal bevacizumab as compared with conventional laser therapy for stage 3+ ROP when both zones I and II are considered
STOP-ROP	US multicenter STOP-ROP	1994–1999			Prospective, randomized, controlled	Use of supplemental oxygen with pulse oximetry saturations of 96%–99% did not cause additional progression of prethreshold ROP. But it also did not significantly reduce the number of infants requiring peripheral ablation surgery.
Reynolds	US Multicenter LIGHT-ROP	1995–1997	<31 weeks	<1,251 g	Prospective, randomized, controlled	A reduction in the ambient light exposure does not alter the incidence of ROP.
BOOST II	UK, Australia, New Zealand	2006–2010	<28 weeks	<1,100 g	Prospective, randomized, controlled	Targeting of oxygen saturation monitoring at levels <90% was associated with an increased death rate

BW, birth weight; ROP, retinopathy of prematurity.

PARENT VOICES

Jennifer Degl

Retinopathy of prematurity (ROP) had not been on my radar for the first 2 months that my baby was in the NICU. I had spent my time researching about what things could take her life and how to watch for signs and help prevent her from developing those complications. Once she was a few months old and relatively stable and the doctors told me that she had passed the window of time where I had to be afraid every day, I was informed that she would likely develop an eye condition called ROP. All that was explained to me initially was that ROP is a disease of premature babies that causes abnormal blood vessels to grow in the retina. This growth can cause the retina to detach from the back of the eye, leading to blindness and that high levels of oxygen given to preemies exaggerate this condition. How is it that oxygen, needed for survival, can cause babies to go blind? It really does not make sense, but it is so. At first my daughter had her eyes checked at the bedside every week, beginning at 8 weeks old. The eye specialist (pediatric ophthalmologist) told me that my daughter had between stage 3 and 4 ROP and that there was nothing to do but wait and try to lower her oxygen levels as much as possible, but that was not up to me. A few weeks later she had developed stage 4 ROP. I was so afraid that my daughter would have tunnel vision or go completely blind and there was nothing I could do about it. When my daughter was a little over 3 months old, the doctor told me that her ROP was improving. Each week it continued to improve and she was discharged from the NICU with only stage 1 ROP. We were instructed to follow up with a pediatric ophthalmologist. We saw the pediatric ophthalmologist every month for 1 year and then every 3 months and then every 6 months, and now we only go once a year. Today, at 6 years old, my daughter is cleared of ROP and only needs to wear glasses when she colors, reads, or does any close-up work.

ONLINE RESOURCES

Family Practice Notebook. (n.d.). *Conjunctivitis in newborns*. Retrieved from https://fpnotebook.com/Eye/NICU/CnjnctvtsInNwbrns.htm

Family Practice Notebook. (n.d.). *Newborn eye exam*. Retrieved from http://www.fpnotebook.com/Nicu/Exam/NwbrnEyExm.htm

University of Illinois Department of Ophthalmology. (n.d.). *Eye conditions and treatments*. Retrieved from https://eyecare.uic.edu/eyeConditions/index.shtml

REFERENCES

Allegaert, K., deCoen, K., & Devilieger, H.; on behalf of the EpiBel Study Group. (2004). Threshold retinopathy at threshold of viability: The EpiBel study. *British Journal of Ophthalmology, 88*(2), 239–242. doi:10.1136/bjo.2003.027474

American Academy of Pediatrics. (2018). In D. W. Kimberlin, S. S. Long, M. T. Brady, & Jackson (Eds.), *Red Book 2018–2021 Report of the Committee on Infectious Diseases. Section 5: Antimicrobial prophylaxis, prevention of neonatal ophthalmia* (31st ed., pp. 1046–1049). Elk Grove, IL: Author.

Anderson, C. G., Benitz, W. E., & Madan, A. (2004). Retinopathy of prematurity and pulse oximetry: A national survey of recent practices. *Journal of Perinatology, 24*, 164–168. doi:10.1038/sj.jp.7211067

Attar, M. A., Gates, M. R., Iatrow, A. M., Lang, S. W., & Bratton, S. L. (2005). Barriers to screening infants for retinopathy of prematurity after discharge or transfer from a neonatal intensive care unit. *Journal of Perinatology, 25*(1), 36–40. doi:10.1038/sj.jp.7211203

BOOST II Collaborative Groups-United Kingdom, Australia, & New Zealand. (2013). Outcome saturations and outcomes in preterm infants. *The New England Journal of Medicine, 368*, 2094–2104. doi:10.1056/NEJMoa1302298

Brown, A. M., Lindsey, D. T., Cammenga, J. G., Giannone, P. J., & Stenger, M. R. (2015). The contrast sensitivity of the newborn human infant. *Investigative Ophthalmology and Visual Science, 56*, 625–632. doi:10.1167/iovs.14-14757

Brown, M. M., & Brown, G. C. (2005). How to interpret a healthcare economic analysis. *Current Opinion in Ophthalmology, 16*(3), 191–194. doi:10.1097/01.icu.0000164166.55550.68

Brown, M. M., Brown, G. C., & Sharma, S. (2004). Value-based medicine and vitreoretinal diseases. *Current Opinion in Ophthalmology, 15*(3), 167–172. doi:10.1097/01.icu.0000120675.27548.d5

Burd, L. (2016). Fetal alcohol spectrum disorder: Complexity from comorbidity. *The Lancet, 387*(10022), 926–927. doi:10.1016/S0140-6736(15)01346-X

Cagini, C., Tosi, G., Stracci, F., Rinaldi, V. E., & Verotti, A. (2017). Red reflex examination in neonates: Evaluation of 3 years of screening. *International Ophthalmology, 37*(5), 1199–1204. doi:10.1007/s10792-016-0393-2

Chacon-Cruz, E., Alvelais-Palacios, J. A., Rodriguez-Valencia, J. A., Lopatynsky-Reyes, E. Z., Volker-Sobernanes, M. L., & Rivas-Landeros, R. M. (2017). Meningococcal neonatal purulent conjunctivitis/sepsis and asymptomatic carriage of *N. meningitides* in mother's vagina and both parents' nasopharynx. *Case Reports in Infectious Diseases, 2017*. doi:10.1155/2017/6132857

Chawla, D., Agarwal, R., Deorari, A., Paul, V. K., Parijat, C., & Azad, R. V. (2012). Retinopathy of prematurity. *Indian Journal of Pediatrics, 79*(4), 501–509. doi:10.1007/s12098-010-0279-7

Chen, J., & Smith, L. E. H. (2007). Retinopathy of prematurity. *Angiogenesis, 10*(2), 133–140. doi:10.1007/s10456-007-9066-0

Chorna, O. D., Guzzetta, A., & Maitre, N. L. (2017). Vision assessments and interventions for infants 0-2 years at high risk for cerebral palsy: A systematic review. *Pediatric Neurology, 76*, 3–13. doi:10.1016/j.pediatrneurol.2017.07.011

Chow, L. C., Wright, K. W., & Sola, A.; The CSMC Oxygen Administration Study Group. (2003). Can changes in clinical practice decrease the incidence of severe retinopathy of prematurity in very low birth weight infants? *Pediatrics, 111*(2), 339–345. doi:10.1542/peds.111.2.339

Coats, D. K., & Reddy, A. K. (2009). Retinopathy of prematurity. In M. E. Wilson, R. Trivedi, & R. Saunders (Eds.), *Pediatric ophthalmology* (pp. 376–384). Berlin, Germany: Springer-Verlag.

Cooke, R. W. I., Foulder-Hughes, L., Newsham, D., & Clarke, D. (2004). Ophthalmic impairment at 7 years of age in children born very

preterm. *Archives of Diseases in Childhood—Fetal-Neonatal Edition, 89*(3), F249–F252. doi:10.1136/adc.2002.023374

Darlow, B. A., Hutchinson, J. L., Henderson-Smart, D. J., Donoghue, D. A., Simpson, J. M., & Evans, N. J.; The Australian and New Zealand Neonatal Network. (2005). Prenatal risk factors for severe retinopathy of prematurity among very preterm infants of the Australian and New Zealand Neonatal Network. *Pediatrics, 115*(4), 990–996. doi:10.1542/peds.2004-1309

Davitt, B. V., Dobson, V., Good, W. V., Hardy, R. J., Quinn, G. E., Siatkowski, R. M., . . . Tung, B.; The Early Treatment for ROP Cooperative Group. (2005). Prevalence of myopia at 9 months in infants with high-risk prethreshold retinopathy of prematurity. *Ophthalmology, 112*(9), 1564–1568. doi:10.1016/j.ophtha.2005.03.025

de Alba Campomanes, A. G., & Binenbaum, G. (2018). Eye and vision disorders In C. A. Gleason & S. E. Juul (Eds.), *Avery's diseases of the newborn* (10th ed., pp. 1536–1557). Philadelphia, PA: Elsevier.

de Miranda, H. A., Costa, M. C., Frazao, M. A. M., Simao, N., Franchischini, S., & Moshfeghi, D. M. (2016, August). Expanded spectrum of congenital ocular findings in microcephaly with presumed zika infection. *Ophthalmology, 123*(8), 1788–1794. doi:10.1016/j.ophtha.2016.05.001

Drack, A. (2006). Retinopathy of prematurity. *Advances in Pediatrics, 53*(1), 211–226. doi:10.1016/j.yapd.2006.04.010

Early Treatment for Retinopathy of Prematurity Cooperative Group. (2003). Revised indications for the treatment of retinopathy of prematurity: Results of the early treatment for retinopathy of prematurity randomized trial. *Archives of Ophthalmology, 121*(12), 1684–1694. doi:10.1001/archopht.121.12.1684

Early Treatment for Retinopathy of Prematurity Cooperative Group. (2005). The incidence and course of retinopathy of prematurity: Findings from the early treatment for retinopathy of prematurity study. *Pediatrics, 115*(1), 15–23. doi:10.1542/peds.2004-1413

Ertzbischoff, L. M. (2004). A systematic review of anatomical and visual function outcomes in preterm infants after scleral buckle and vitrectomy for retinal detachment. *Advances in Neonatal Care, 4*(1), 10–19. doi:10.1016/j.adnc.2003.11.009

Ewart-Toland, A., Yankowitz, J., Winder, A., Imagire, R., Cox, V. A., Aylsworth, A. S., & Golabi, M. (2000). Oculoauriculovertebral abnormalities in children of diabetic mothers. *American Journal of Medical Genetics, 90*(4), 303–309. doi:10.1002/(SICI)1096-8628(20000214)90:4<303::AID-AJMG8>3.0.CO;2-Q

Fierson, W. M., & American Academy of Pediatrics Section on Ophthalmology, American Academy of Ophthalmology, American Association for Pediatric Ophthalmology & Strabismus, American Association of Certified Orthoptists. (2018). Screening examination of premature infants for retinopathy of prematurity. *Pediatrics, 142*(6), e20183061.

Fleck, B. W., & McIntosh, N. (2009). Retinopathy of prematurity: Recent developments. *NeoReviews, 10*(1), e20–e30. doi:10.1542/neo.10-1-e20

Hård, A. L., & Hellström, A. (2011). On safety, pharmacokinetics and dosage of bevacizumab in ROP treatment–a review. *Acta Paediatrica, 100*(12), 1523–1527. doi:10.1111/j.1651-2227.2011.02445.x

Hylander, M. A., Strobino, D. M., Pessullo, J. C., & Dhanireddy, R. (2001). Association of human milk feedings with a reduction in retinopathy of prematurity among very low birth weight infants. *Journal of Perinatology, 21*(6), 356–362. doi:10.1038/sj.jp.7210548

International Committee for the Classification of Retinopathy of Prematurity. (2005). The international classification of retinopathy of prematurity revisited. *Archives of Ophthalmology, 123*(7), 991–999. doi:10.1001/archopht.123.7.991

Jacobson, L. K., & Dutton, G. N. (2000). Periventricular leukomalacia: An important cause of visual and ocular motility dysfunction in children [review]. *Survey of Ophthalmology, 45*(1), 1–13. doi:10.1016/S0039-6257(00)00134-X

Jacobson, L. K., Ygge, J., Flodmark, O., & Ek, U. (2002). Visual and perceptual characteristics, ocular motility and strabismus in children with periventricular leukomalacia. *Strabismus, 10*(2), 179–183. doi:10.1076/stra.10.2.179.8132

Jampol, L. M., & Goldstein, D. A. (2016). Zika virus infection and the eye. *JAMA Ophthalmology, 134*(5),535–536. doi:10.1001/jamaophthalmol.2016.0284

James, S.H. & Kimberlin, D.W. (2015). Neonatal herpes simplex virus infection: epidemiology and treatment. *Clinical Perinatology, 42*(1), 47–59.

Jefferies, A. L. (2016). Retinopathy of prematurity: An update on screening and management. *Paediatric Child Health, 21*(2), 101–104. doi:10.1093/pch/21.2.101

Johnson, P. J. (2015). Head, eyes, ears, nose, mouth, and neck assessment. In E. P. Tappero & M. E. Honeyfield (Eds.), *Physical assessment of the newborn* (5th ed., pp. 61–78). Petuluma, CA: NICU Ink Books.

Jones, K. L., Jones, M. C., & Casanelles, M. D. C. (2013). *Smith's recognizable patterns of human malformation* (7th ed., pp. 933f–936f). Philadelphia, PA: Saunders.

Kaya, M., Berk, A. T., & Yaman, A. (2017). Long-term evaluation of refractive changes in eyes of preterm children: A 6-year follow-up study. *International ophthalmology 38*(4), 1681–1688. doi:10.1007/s10792-017-0642-z

Khahaeni, L. M. (2017). Ocular complications of congenital infections. *NeoReview, 18*(2), e100–e104. doi:10.1542/neo.18-2-e100

Kinori, M., Schwartzstein, H., Zeid, J. L., Kurup, S. P., & Mets, M. B. (2018). Congenital lymphocytic choriomeningitis virus—An underdiagnosed fetal teratogen. *Journal of American Association for Pediatric Ophthalmology and Strabismus, 22*(1), 79–81.e1. doi:10.1016/j.jaapos.2017.08.011

Laghmari, M., Skiker, H., Handor, H., Mansouri, B., Ouazzani Chahdi, K., Lachkar, R., . . . Daoudi, R. (2014). Birth-related retinal hemorrhages in the newborn: Incidence and relationship with maternal, obstetric and neonatal factors. Prospective study of 2,031 cases. *Journal Francais d'Ophtalmologie, 37*(4), 313–319. doi:10.1016/j.jfo.2013.06.005

Larsson, E. K., Rydberg, A. C., & Holmstrom, G. E. (2005). A population-based study on the visual outcome in 10-year-old preterm and full-term children. *Archives of Ophthalmology, 123*, 825–832. doi:10.1001/archopht.123.6.825

Mabry-Hernandez, I., & Oliverio-Hoffman, R. (2010). *Ocular prophylaxis for gonococcal ophthalmia neonatorum: Evidence update for the U.S. Preventive Services Task Force reaffirmation recommendation statement*. Retrieved from http://www.uspreventiveservicestaskforce.org/uspstf10/gonoculproph/gonocup.htm#ref12

Mandelbrot, L. (2012). Fetal varicella—Diagnosis, management, and outcome. *Prenatal Diagnosis, 32*(6), 511–518. doi:10.1002/pd.3843

Martins, E. N., & Morse, L. S. (2005). Evaluation of Internet websites about retinopathy of prematurity patient education. *British Journal of Ophthalmology, 89*(5), 565–568. doi:10.1136/bjo.2004.055111

McAuley, J. B. (2014). Congenital toxoplasmosis. *Journal of the Pediatric Infectious Diseases Society, 3*(Suppl. 1), S30–S35. doi:10.1093/jpids/piu077

Mestan, K. K., Marks, J. D., Hecox, K., Huo, D., & Schreiber, M. D. (2005). Neurodevelopmental outcomes of premature infants treated with inhaled nitric oxide. *New England Journal of Medicine, 353*, 23–32. doi:10.1056/NEJMoa043514

Mintz-Hittner, H. A., Kennedy, K. A., & Chuang, A. Z.; for the BEAT-ROP Coorperative Group. (2011). Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. *New England Journal of Medicine, 364* (7), 603–615. doi:10.1056/NEJMoa1007374

Nash, A., & Davies, L. (2017). Fetal alcohol spectrum disorders: What pediatric providers need to know. *Journal of Pediatric Health Care, 31*(5), 594–606. doi:10.1016/j.pedhc.2017.04.002

O'Connor, M. T., Vohr, B. R., Tucker, R., & Cashore, W. (2003). Is retinopathy of prematurity increasing among infants less than 1250 g birth weight? *Journal of Perinatology, 23*, 673–678. doi:10.1038/sj.jp.7211008

O'Keefe, M., Kafil-Hussain, N., Flitcroft, I., & Lanigan, B. (2001). Ocular significance of intraventricular haemorrhage in premature infants. *British Journal of Ophthalmology, 85,* 357–359. doi:10.1136/bjo.85.3.357

O'Neil, E. (2011, May 4). Effects of prenatal alcohol exposure on ocular development. *Embryo project encyclopedia*. Retrieved from https://embryo.asu.edu/pages/effects-prenatal-alcohol-exposure-ocular-development

Örge, F. H., & Grigorian, F. (2015). Part 20: The eye. Examination and common problems of the neonatal eye. In R. J. Martin, A. A. Fanaroff, & M. C. Walsh (Eds.), *Fanaroff & Martin's neonatal-perinatal medicine: Diseases of the fetus and infant* (10th ed.). Philadelphia, PA: Elsevier.

Pineles, S. L., & Isenberg, S. J. (2016). Eye disorders. In M. G. MacDonald & M. M. K. Seshia (Eds.), *Avery's neonatology: Pathophysiology and management of the newborn* (7th ed., pp. 1061–1073). Philadelphia, PA: Wolters Kluwer.

Purewal, R., Costello, L., Garlapati, S., Mitra, S, Mitchell, M., & Moffett, K. S. (2016). Congenital herpes simplex virus in the newborn: A diagnostic dilemma. *Journal of the Pediatric Infectious Diseases Society, 5*(3), e21–e23. doi:10.1093/jpids/piw013

Reynolds, J. D. (2010). Retinopathy of prematurity. *International Ophthalmology Clinics, 50*(4), 1–13. doi:10.1097/IIO.0b013e3181f12ffd

Reynolds, J. D., Dobson, V., Quinn, G. E., Fielder, A. R., Plamer, E. A., Saunders, R. A., …Tung, B.; for the CRYO-ROP & LIGHT-ROP Coorperative Groups. (2002). Evidenced-based screening criteria for retinopathy of prematurity, natural history data from the CRYO-ROP and LIGHT-ROP studies. *Archives of Ophthalmology, 120*(11), 1470–1476. doi:10.1001/archopht.120.11.1470

Reynolds, J. D., Hardy, R. J., Kennedy, K. A., Spencer, R., van Heuven, W. A., & Fielder, A. R. (1998). Lack of efficacy of light reduction in preventing retinopathy of prematurity. *New England Journal of Medicine, 338*, 1572–1576. doi:10.1056/NEJM199805283382202

Roth, D. B., Morales, D., Feuer, W. J., Hess, D., Johnson, R. A., & Flynn, J. T. (2001). Screening for retinopathy of prematurity employing the RetCam 120: Sensitivity and specificity. *Archives of Ophthalmology, 119*(2), 268–272. Retrieved from https://jamanetwork.com/journals/jamaophthalmology/article-abstract/265424

Royal College of Ophthalmologists. (2008). *Guideline for the screening and treatment of retinopathy of prematurity*. Retrieved from https://www.rcophth.ac.uk/wp-content/uploads/2014/12/2008-SCI-021-Guidelines-Retinopathy-of-Prematurity.pdf

Russo, F. B., & Beltrao-Braga, P. C. B. (2017). The impact of Zika virus in the brain. *Biochemical and Biophysical Research Communications, 492*, 603–607. doi:10.1016/j.bbrc.2017.01.074

Sankar, M. J., Sankar, J., Mehta, M., Bhat, V., & Srinivasan, R. (2016). Anti-vascular endothelial growth factor (VEGF) drugs for treatment of retinopathy of prematurity. *Cochrane Database of Systematic Reviews*, (2), CD009734. doi:10.1002/14651858.CD009734.pub2

Saugstad, O. D. (2005). Oxygen for newborns: How much is too much? *Journal of Perinatology, 25*(Suppl. 2), S45–S49. doi:10.1038/sj.jp.7211321

Scanlon, J. W., Nelson, T., Grylack, L. J., & Smith, Y. F. (1979). *A system of newborn physical examination*. Baltimore, MD: University Park Press.

Schoenwolf, G. C., Bleyl, S. B., Brauer, P. R., & Francis-West, P. H. (2015). *Larsen's human embryology* (5th ed.). Philadelphia, PA: Elsevier.

Shah, P. K., Prabhu, V., Karandikar, S. S., Ranjan, R., Narendran, V., & Kalpana, N. (2016). Retinopathy of prematurity: Past, present, and future. *World Journal of Clinical Pediatrics, 5*(1), 35–46. doi:10.5409/wjcp.v5.i1.35

Smith, L. E. (2003). Pathogenesis of retinopathy of prematurity. *Seminars in Neonatology, 8*(6), 469–473. doi:10.1016/S1084-2756(03)00119-2

Smith, L. E. (2004). Pathogenesis of retinopathy of prematurity. *Growth Hormone and IGF Research, 14*(Suppl. A), S140–S144. doi:10.1016/j.ghir.2004.03.030

Stahl, A., Krohne, T. U., Eter, N., Oberacher-Velten, I., Guthoff, R., Meltendorf, S., . . . Walz, J. M. (2018). Comparing alternative ranzibizumab dosages for safety and efficacy in retinopathy of prematurity: A randomized clinical trial. *Journal of the American Medical Association Pediatrics, 172*(3), 278–286. doi:10.1001/jamapediatrics.2017.4838

Stewart, J. E., Hernandez, F., & Duncan, A. F. (2017). Follow-up care of very preterm and very low birth weight infants. In E. C. Eichenwalk, A. R. Hanson, C. R. Martin, & S. R. Stark (Eds.), *Cloherty and Stark's manual of neonatal care* (8th ed., pp. 192–201). Philadelphia, PA: Wolters Kluwer.

Trigler, L., Weaver, R. G., O'Neil, J. W., Barondes, M. J., & Freedman, S. F. (2005). Case series of angle-closure glaucoma after laser treatment for retinopathy of prematurity. *Journal of the American Association for Pediatric Ophthalmology and Strabismus, 9*(1), 17–21. doi:10.1016/j.jaapos.2004.10.007

Wang, R., Martinez-Frias, M. L., & Graham, J. M. (2002). Infants of diabetic mother are at increased risk for the oculo-auriculo-vertebral sequence: A case-based and case-control approach. *Journal of Pediatrics, 141*(5), 611–617. doi:10.1067/mpd.2002.128891

Watts, P., Maguire, S., Kwok, T., Talabani, B., Mann, M., Wiener, J., . . . Kemp, A. (2013). Newborn retinal hemorrhages: A systematic review. *Journal of American Association for Pediatric Ophthalmology and Strabismus, 17*(1), 70–78. doi:10.1016/j.jaapos.2012.07.012

Wood, M. G., & Kaufman, L. M. (2009). Apnea and bradycardia in two premature infants during routine outpatient retinopathy of prematurity screening. *Journal of the American Association for Pediatric Ophthalmology and Strabismus, 13*, 501–503. doi:10.1016/j.jaapos.2009.04.008

York, J. R., Landers, S., Kirby, R. S., Arbogast, P. G., & Penn, J. S. (2004). Arterial oxygen fluctuation and retinopathy of prematurity in very-low-birth-weight infants. *Journal of Perinatology, 24*, 82–87. doi:10.1038/sj.jp.7211040

Zhu, X., Zhao, R., Wang, Y., Ouyang, L., Yang, J., Li, Y., & Pi, L. (2017). Refractive state and optical compositions of preterm children with and without retinopathy of prematurity in the first 6 years of life. *Medicine, 96(*45), e8565–e8570. doi:10.1097/MD.0000000000008565

Zloto, O., Gharaibeh, A., Mezer, E., Stankovic, B., Isenberg, S., & Wygnanski-Jaffe, T. (2016). Ophthalmia neonatorum treatment and prophylaxis: IPOSC global study. *Graefes Archive for Clinical and Experimental Ophthalmololgy, 254*(3), 577–582. doi:10.1007/s00417-016-3274-5

CHAPTER 18

Genitourinary System

Leslie A. Parker

INTRODUCTION

Comprehensive nursing care of infants with renal or genital disorders requires a thorough understanding of normal anatomy and physiology. Development of renal and genital systems arises from shared structures; therefore, abnormalities in one system may indicate abnormal development in the other. Because nurses provide hands-on care to infants in both the newborn nursery and neonatal intensive care unit (NICU), they are often the first to recognize abnormalities in the renal and genital systems. To readily identify such disorders and participate in their collaborative management, nurses need a clear understanding of the normal anatomy and physiology of the genital and renal systems and the pathological processes that may be present in the neonatal patient.

The kidneys function to maintain fluid, electrolyte, and acid–base balance as well as to rid the body of nitrogenous and other waste products. Perinatal depression, prematurity, medical management for common neonatal conditions, and dehydration are only a few of the many factors placing the newborn at risk for renal compromise. Timely, accurate nursing assessment and intervention is of utmost priority to ensure an optimal outcome for both infants and their families.

This chapter outlines embryological development and anatomy, physiology, and assessment of the genitourinary (GU) system. It also describes various abnormalities and disease processes commonly identified in the neonatal period, including pathophysiology, risk factors, clinical manifestations, diagnosis, collaborative management, and prognosis.

EMBRYOLOGICAL DEVELOPMENT OF THE UROGENITAL SYSTEM

During the first weeks of gestation, the mesoderm is divided into three segments: lateral, intermediate, and paraxial. The intermediate mesoderm separates from the paraxial mesoderm and migrates ventrally as the nephrogenic cords located on either side of the primitive aorta. Cells on the dorsal end of the nephrogenic cords join to form the urogenital ridges from which components of both the urinary and genital structures are developed.

The Urinary System

The urinary system consists of the kidneys, ureters, urinary bladder, and the urethra. Development of the primary excretory organ begins around the fourth week of gestation with the production of fetal urine by week 10. At approximately 36 weeks, renal anatomic development is completed. Functional maturity increases after birth and continues until approximately 2 years of age.

Development of the kidneys occurs with the progressive formation of three nephric structures within the nephrogenic cord: the pronephros, the mesonephros, and the metanephros. The pronephros or primitive kidney develops during the first month of gestation and then gradually degenerates, thus contributing the duct system for the next developmental stage. The pronephros has no excretory function.

The second excretory organ to develop is the mesonephros. Mesonephric development begins at the caudal end of the pronephros during the fourth to sixth weeks of gestation. The mesonephros contains thin-walled glomeruli and functional tubules. Ultra-urine is produced by these mesonephric nephrons at 8 to 10 weeks. Mesonephric nephrons that are located more cranially along the nephrogenic cord begin to degenerate as those located more caudally are still developing. During this time, approximately the fourth week, the gonadal blastema begins to form in the genital ridge located on the medial aspect of each mesonephros, thus creating a urogenital ridge between the developing kidney and the genitals. As the mesonephric structure begins to degenerate in a caudal direction, it leaves a duct system for the following stage. In addition, the mesonephric duct eventually matures into the epididymis, vas deferens, and ejaculatory duct in the male or the vestigial Garner in the female. Thus, failure of the mesonephric duct to develop may result in anomalies in both the urinary and genital systems.

The third and final stage of kidney development, beginning in the fifth week of gestation, is the formation of the metanephros or definitive kidney. The metanephros develops from induction of the metanephrogenic blastema (metanephric mesoderm) by the ureteric bud. The ureteric bud, also called the metanephric diverticulum, is an outgrowth of the mesonephric duct, and the metanephrogenic blastema originates from the lower segment of the nephrogenic cord. As this stage progresses, the stalk of ureteric bud becomes the ureter. The development of the renal pelvis, major and minor calices, and, finally, the collecting tubes occurs through the continued elongating and branching of the cranial end of the ureteric bud. At the ends of the collecting tubules, the cells of the metanephric blastema clump and stimulate the formation of the glomerulus, proximal tubule, loop of Henle, and distal tubule,

which, eventually, empties into the collecting duct, thereby forming a nephron (Moore, Persaud, & Torchia, 2016).

To complete formation of the urinary system, a bladder and urethra are formed. The epithelium of the bladder and most of the urethra derive from the embryological hindgut. The expanded terminal end of the hindgut is the cloaca. The allantois, an outgrowth of the yolk sac, is attached to the ventral side of the cloaca. The urorectal septum creates a compartmentalized cloaca that consists of the anorectal canal and the urogenital sinus. With the exception of the bladder trigone—the area between the urethra and the ureters—the bladder arises from this urogenital sinus. The primitive structures regress, fibrose, or become part of the newly formed structures. The point of origin of the ureteric bud marks the point of insertion for the ureters. The ureters, formerly the metanephric ducts, then open bilaterally into the urinary bladder as the developing bladder reabsorbs the distal portions of the mesonephric ducts into its dorsal wall (trigone).

The allantois narrows into a fibrous band called the urachus that runs from the apex of the bladder to the umbilicus. Abnormalities of the urachus occur when it either remains patent or forms an urachal sinus. A patent urachus may occur in association with other anomalous conditions and may allow development of a functional kidney by alleviating the effects of urinary obstruction. An urachal sinus is usually an isolated anomaly and causes leakage of urine from the umbilical stump.

Urethral development in the male and female begins in the same manner. The urogenital sinus is visible at 6 weeks and consists of a narrow portion near the bladder, the pelvic urethra, and an expanded portion near the urogenital membrane (cloacal membrane), called the phallic urethra. Through several processes and stages, the phallic end of the urogenital sinus eventually becomes the bulbar and the penile urethra, and the pelvic urethra develops into the permanent urethra and vagina. Differentiation of the urethra in the male and female fetus can be detected by 12 to 14 weeks' gestation.

Initially, the kidneys are located within the pelvic region. They make a gradual ascent into their final location in the flank position or lumbothoracic area. Normal renal ascent is achieved as the result of caudal growth of the fetal spine, lengthening of the ureter, molding of the renal parenchyma, and fixation of the kidney to the retroperitoneum (Moore et al., 2016). Failure of normal ascent of the kidneys results in abnormalities such as horseshoe kidneys or pelvic kidneys. Blood supply to the ascending kidneys changes from lower arteries that gradually regress to arteries that arise from the aorta.

In utero, the placenta functions as the excretory organ for the fetus. Functional kidneys are, therefore, not necessary for fetal homeostasis. Consequently, pathological problems such as aplastic, hypoplastic, and otherwise nonfunctioning kidneys may not be detected until after birth. Fetal urination, swallowing, and breathing all impact amniotic fluid volume. Excretion of fetal urine contributes significantly to amniotic fluid volume, especially during the third trimester. A reduction in fetal urine excretion results in oligohydramnios. Failure of the fetus to swallow amniotic fluid due to gastrointestinal obstruction or central nervous system anomaly results in overaccumulation of amniotic fluid or polyhydramnios. Abnormalities in amniotic fluid volume can, therefore, signal pathology in various fetal organ systems.

A balance between genetic influences, cellular mediators, and the interaction of various molecular mechanisms is necessary for kidney development. Depending on the timing of development, insult or failure of the primitive structures to grow or to branch appropriately may result in a variety of uropathies, including dysplasia and renal agenesis.

PHYSIOLOGY OF KIDNEY FUNCTION

Kidney structure includes the cortex, the major and minor calices, and the renal pelvis (Figure 18.1). The kidney is divided into two sections: the outer renal cortex and the inner medulla. The kidney functions to regulate fluid and electrolyte balance and arterial blood pressure, as well as to excrete toxic and waste substances. These regulatory mechanisms are intimately tied to the formation of urine that involves three basic processes: ultrafiltration of plasma by the glomerulus, reabsorption of water and solutes from the ultrafiltrate, and secretion of certain solutes into the tubular fluid (Koeppen & Stanton, 2013).

The nephron is the functional unit of the kidney and is the site of urine formation. It consists of a glomerulus (Bowman's capsule and glomerular capillaries) and a renal tubule that has three sections: a proximal convoluted tubule, the loop of Henle, and a distal convoluted tubule (Figure 18.2). After urine is produced by the nephron, it drains into the minor and major calyces. From there, it drains into a single large cavity called the renal pelvis, then out through the ureter, and finally into the bladder.

Nephron formation (nephrogenesis) begins during the second month of gestation and is anatomically complete by approximately 35 weeks. Although anatomic formation may be complete, functional immaturity of the nephrons continues throughout infancy. At the completion of nephrogenesis, each kidney contains approximately 1 million nephrons. Nephrogenesis begins deep within the renal cortex near the medulla in the juxtamedullary region and continues outwardly (Koeppen & Stanton, 2013). The juxtamedullary nephrons differ from the superficial cortical nephrons in that their glomeruli are larger, the loop of Henle is longer, and the efferent arteriole forms a more complex vascular system. The less mature superficial cortical nephrons make up the majority of nephrons, whereas the more mature juxtamedullary nephrons account for a very small percentage of the total number. Altered renal function in the premature infant may, therefore, be caused by both anatomic and physiological immaturity.

RENAL BLOOD FLOW

Urine formation begins with blood flow. The pressure-driven process of ultrafiltration depends on optimal arterial pressure and is regulated by the dilation and constriction of afferent and efferent arterioles (Koeppen & Stanton, 2013). Adequate renal blood flow

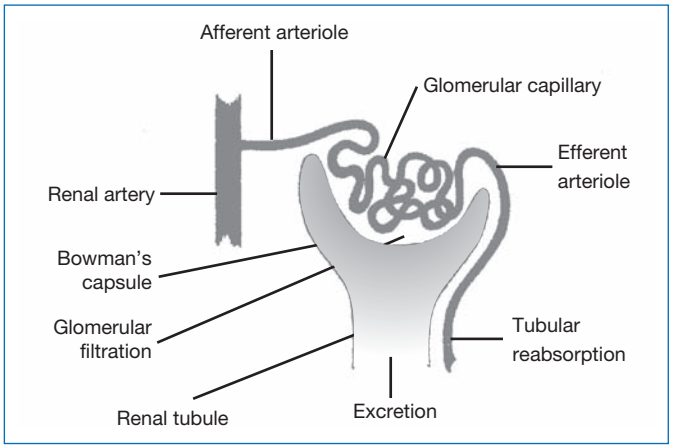

FIGURE 18.1 Glomerular apparatus.

Source: From Guyton, A. C., & Hall, J. E. (1997). *Human physiology and mechanisms of disease* (6th ed.). Philadelphia, PA: Saunders.

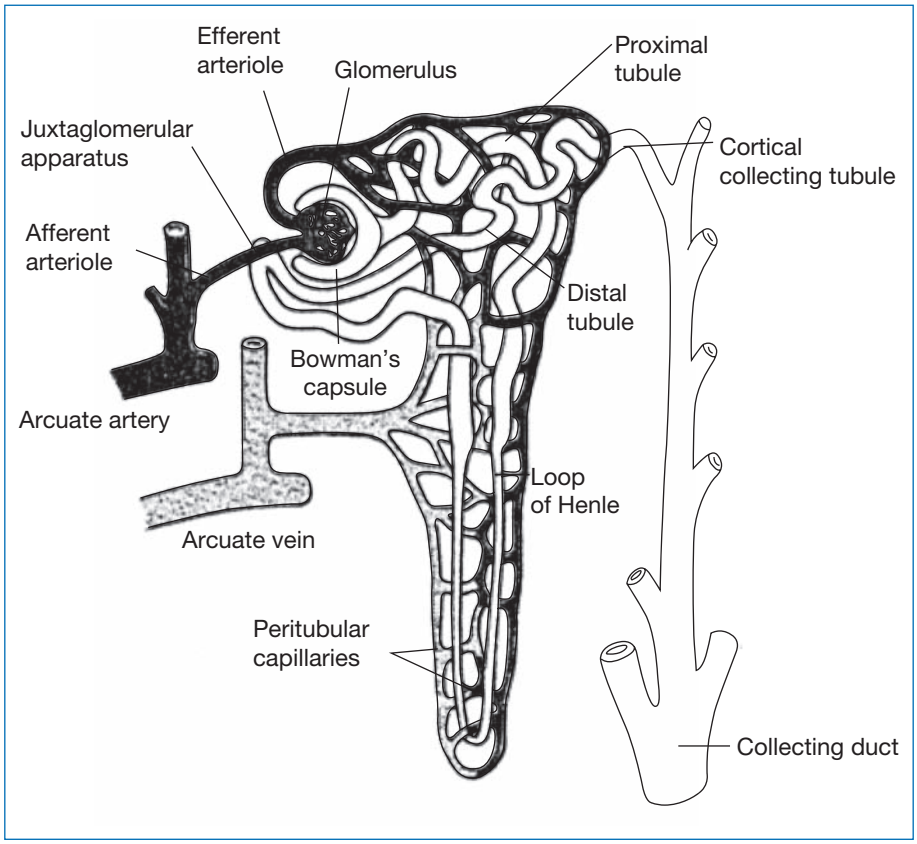

FIGURE 18.2 Anatomy of the nephron.

Source: From Guyton, A. C., & Hall, J. E. (1997). *Human physiology and mechanisms of disease* (6th ed.). Philadelphia, PA: Saunders.

is, therefore, essential to renal function. During the first 12 hours of life, 4% to 6% of the cardiac output goes to the kidney, which increases to 8% to 10% over the next few days. This is compared to the 25% of cardiac output that reaches the adult kidney. Renal blood flow not only provides oxygen and nutrients to the kidneys but also affects the rate of solute and water reabsorption by the proximal tubule, participates in the concentration and dilution of the urine, and delivers substrates for excretion in the urine.

The left and right renal arteries arise from the aorta. After entering the kidneys, they divide and branch several times to eventually give rise to the afferent arterioles. Each nephron receives one afferent arteriole that divides and forms the glomerulus. The distal ends of the glomerular capillaries merge to form the efferent arterioles that carry blood away from the glomerulus. The efferent arterioles divide to form the peritubular capillaries, which surround the tubular parts of the nephron in the renal cortex. Other vessels called the vasa recta also arise from the efferent arterioles to surround the tubular parts of the nephron in the renal medulla. The peritubular capillaries empty into the venous system and eventually leave the kidneys in the form of the renal vein. The fetus and infant have a decreased renal blood flow due to increased renal vascular resistance and decreased mean arterial pressure. Renal vascular resistance is elevated in the fetus because fetal renal function is required only for production of amniotic fluid (Blackburn, 2013). Renal blood flow increases with both advancing gestational and chronological age.

GLOMERULAR FILTRATION RATE

As blood flows into the kidney via the renal artery, it is directed into the afferent arteriole and carried into the glomerulus. The glomerulus consists of the glomerular capillaries and Bowman's capsule. Plasma driven through the glomerular capillaries is filtered through the filtration barrier, and the protein-free plasma, or ultrafiltrate, is forced into the Bowman's capsule or leaves via the efferent arteriole and enters into the renal vein. To produce ultrafiltrate, the glomerulus functions as a filtering site. Glomerular capillaries are lined with epithelial cells called podocytes, forming one of the layers of Bowman's capsule (see Figure 18.2). The endothelial cells of the glomerular capillaries are covered by a basement membrane and also surrounded by podocytes. The basement membrane, podocytes, and the endothelial cells of the glomerular capillaries form the filtration barrier. The epithelial cells of this filtration barrier express negatively charged glycoproteins and contain many small openings called fenestrations. The size of the fenestrations inhibits passage of large proteins, such as blood cells and platelets, but is highly permeable to the passage of water, small solutes, urea, and glucose. In addition, positively charged large proteins are repelled by the cationic cell membrane (Koeppen & Stanton, 2013).

The glomerular filtration rate (GFR) is the rate at which fluid is filtered through the glomerulus. Because it is equal to the sum of all filtration rates of all nephrons in both kidneys, the GFR reflects kidney function and a decrease in GFR signifies renal disease. Oncotic and hydrostatic pressures (Starling forces) drive the ultrafiltration process. Oncotic pressure is osmotic pressure generated by large proteins or colloids. Hydrostatic pressure is pressure exerted by fluids in equilibrium and depends on arterial pressure and vascular resistance (Koeppen & Stanton, 2013). Oncotic pressure in Bowman's space is very near zero because ultrafiltrate is nearly protein free (Dias, Sairam, & Kumarasiri, 2014). Filtration at this level is, therefore, driven by hydrostatic pressure across the glomerular capillaries. Hydrostatic pressure within Bowman's space

and glomerular oncotic pressure oppose glomerular hydrostatic pressure in the capillaries. The GFR is proportional to the sum of hydrostatic and oncotic pressures existing along the renal capillaries multiplied by the ultrafiltration coefficient. The difference between the permeability of the glomerular capillary and the glomerular surface area available for filtration is the ultrafiltration coefficient (Koeppen & Stanton, 2013). GFR is, therefore, affected by changes in arterial blood pressure, vascular resistance, concentration of plasma proteins, and glomerular capillary permeability. Alteration in the permeability of the glomerular capillaries may result from inherent damage to the capillary, thus altering the pore size or changing the electrical charge within the membrane. GFR may also be negatively affected by urinary system obstruction.

Fetal GFR is relatively low due to increased renal vascular resistance and decreased renal blood flow and then rapidly increases during the first few hours following birth. GFR increases with both advancing gestational and chronological age due to increased number and growth of the nephrons and reaches full-term levels by 32 to 35 weeks' gestation (Blackburn, 2013). In the preterm infant, functional maturation is determined by conceptional age, not by postnatal age. When corrected for body surface area, GFR is 10 mL/minute/1.73 m^2 at 28 weeks' gestation and rises to 30 mL/minute/1.73 m^2 at term. GFR does not rise due to an increase in the number of nephrons, but rather it is believed to reflect a decrease in vascular resistance and an increase in glomerular surface area (Luyckx & Brenner, 2010). Even in term infants, GFR is low compared to an older infant or child. This low GFR is adequate in normal circumstances, but in conditions such as sepsis, hypoxia, or the administration of nephrotoxic medications, the GFR may not meet the physiological needs of the infant. Medications administered prenatally can also have detrimental effects on fetal GFR and subsequent neonatal renal function. Examples of these drugs include prostaglandin inhibitors (indomethacin), nonsteroidal anti-inflammatories, diuretics, and antibiotics, especially aminoglycosides and angiotensin-converting enzyme inhibitors (Gubhaju, Sutherland, & Black, 2011).

Assessment of GFR is important in evaluating renal function. One method of assessing GFR is measurement of the renal clearance of a substance. Renal clearance represents a volume of plasma completely cleared of a substance by the kidneys over a specified period of time (Koeppen & Stanton, 2013). Various substances are used as markers for measuring GFR. These substances must have the following characteristics: (a) freely filter across the glomerulus into Bowman's space; (b) not be reabsorbed or secreted by the nephron; (c) not be metabolized or produced by the kidney; and (d) not alter GFR (Koeppen & Stanton, 2013). Several substances including cystatin C and inulin have been used as a marker of GFR (Abitbol et al., 2014). Creatinine, a by-product of muscle metabolism, also meets the marker criteria and is the most commonly used marker for estimating renal function in neonates; however, it may not be the best measure of GFR (Kastl, 2017). Because creatinine readily crosses the placenta, levels obtained during the first week reflect maternal levels (Filler, Guerrero-Kanan, & Alvarez-Elias, 2016; Kastl, 2017). After birth, the GFR in term infants increases as renal blood flow increases and vascular resistance decreases. This increase in function generally occurs over the first week of life and results in a drop in creatinine levels to nearly 0.4 mg/dL, depending on clinical status and gestational age. GFR does not increase as drastically until completion of nephrogenesis. Therefore, premature infants do not demonstrate the same decline in serum creatinine levels as infants born after 36 weeks' gestation (Kastl, 2017). Small increases in serum creatinine levels may indicate a significant decrease in GFR. Monitoring trends in serial creatinine levels may, therefore, render a more accurate evaluation of renal function.

Regulation of renal blood flow and, consequently, GFR is achieved by hormonal and sympathetic nervous system (SNS) influences. The renal vessels, including the afferent and efferent arterioles, are highly innervated by sympathetic nerve fibers. Mild stimulation of the SNS does not cause a change in renal vascular tone. However, under severe physiological stress such as that caused by significant fluid loss, activation of the renal sympathetic nerve fibers causes vasoconstriction of the renal arteries, which, in turn, decreases GFR.

Hormonal control is exerted mainly via activation of the renin–angiotensin–aldosterone system (RAS). The RAS plays a significant role in blood pressure regulation and sodium homeostasis and is found in the fetus, beginning at about 3 months' gestation. Renin is an enzyme found in high levels in the plasma and is produced and stored in specialized cells of the juxtaglomerular apparatus. Newborns have a significantly higher renin level than adults due to the neonate's altered GFR, increased vascular resistance, and decreased renal blood flow.

When renal blood flow is diminished due to decreased arterial pressure, the vessel walls of the afferent arterioles are less stretched and release of renin is stimulated. Release of renin causes production of angiotensin I from angiotensin, which is then converted by angiotensin-converting enzyme to angiotensin II. Angiotensin II stimulates secretion of aldosterone by the adrenal cortex. Aldosterone, in turn, triggers increased reabsorption of sodium and water, thereby increasing extracellular fluid volume and renal perfusion (Figure 18.3). The ultimate goal of the renin–angiotensin cycle is to maintain an adequate systemic blood flow to supply the body's vital organs (Tortora & Derrickson, 2017).

SECRETION AND REABSORPTION

The kidneys control fluid and electrolyte balance by reabsorption and secretion of sodium and water. The four segments of the nephron—the proximal tubule, loop of Henle, distal tubule, and the collecting duct—determine the composition and volume of urine.

Because nephron formation begins in the medullary area, the thin ascending portion of the nephron, which controls reabsorption, is not fully formed in the neonate. By birth, nephron formation has extended from the medullary to the juxtamedullary area. The descending portion of the tubular system, which controls urine secretion, is, therefore, more fully developed than the ascending segment at birth. Thus, a newborn's ability to concentrate urine is decreased because although urine secretion occurs readily, reabsorption is limited. Infants are, therefore, more likely to lose sodium, glucose, and other solutes in their urine. This process is further altered in preterm infants, resulting in possibly significant fluid and electrolyte disturbances.

Tubular reabsorption, secretion, and excretion are closely tied together and function to maintain internal homeostasis and regulate fluids and electrolytes. Tubular reabsorption is the process whereby substances from the tubular lumen move into the capillary system through simple diffusion and active transport. Many of the body's nutrients, electrolytes, and 99% of the filtered water are reabsorbed, thus achieving a balance for continued growth and normal physiological function. Simple diffusion involves movement of substances down a gradient, from an area of higher concentration to an area of lower concentration. Active transport requires energy derived directly from adenosine triphosphate because net movement of substances is against a gradient. Molecular structures may link together to piggyback, or carry one another, across the membrane. Sodium first undergoes simple diffusion across the tubular membrane and then is transported via active transport by the sodium pump into the interstitial fluid. Because

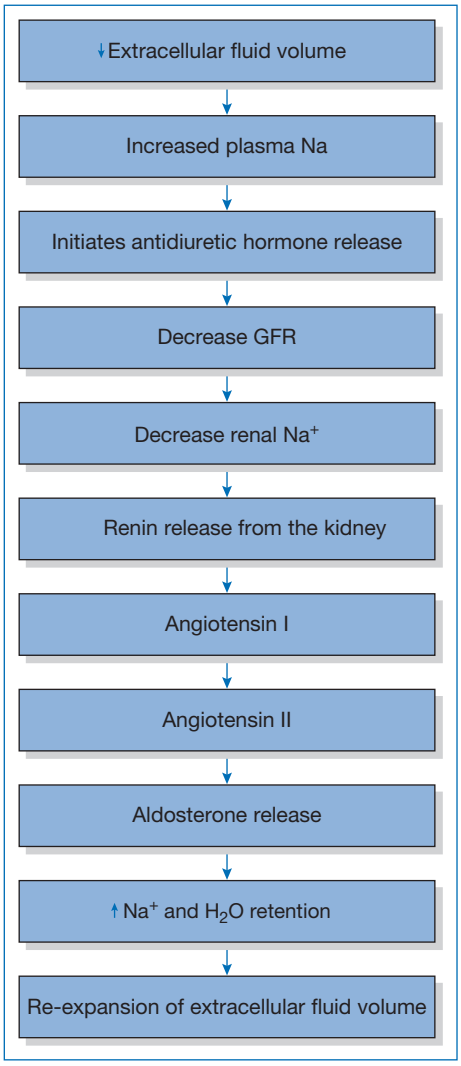

FIGURE 18.3 The renin–angiotensin–aldosterone regulation of extracellular fluid.

GFR, glomerular filtration rate.

sodium filtration depends on GFR, a higher GFR increases sodium reabsorption into the vascular space. If the extracellular fluid volume increases, sodium reabsorption is decreased.

Water follows sodium ions across the membrane and into the capillary bed. This type of transport of a second substance is called secondary active transport. Simple facilitated diffusion is similar to active transport in that a carrier substance is used, but the net movement is not against a gradient. Glucose is a substance that secondary active transport carries along with sodium across the membrane. Glucose is reabsorbed by the proximal tubules, thus appearing in the urine only when the renal threshold or the maximal tubular transport capacity has been exceeded or when the permeability of the filtering capillaries has been altered. Amino acids, water-soluble vitamins, albumin, and lactate are also transported in this manner.

Tubular secretion moves substances such as potassium and hydrogen from the epithelial lining of the tubules' capillaries into the interstitial fluid and, finally, into the tubular lumen. Tubular excretion is the process whereby substances enter the filtrate that will eventually exit the body as urine. Ions such as potassium, which are secreted in the distal tubule (a portion is also reabsorbed in the proximal tubule), find their way into the urine when the body has no need for higher concentration levels. The movement of hydrogen ions influences the excretion of potassium; therefore, metabolic acidosis and alkalosis affect the potassium level. **Quality and Safety: Hormones and drugs, especially diuretics, can also affect the movement of potassium with Aldactone causing potassium secretion and the thiazides resulting in potassium excretion.** Other filtrates present in the urine include urea, creatinine, and other ions not needed by the body.

ASSESSMENT OF THE GENITOURINARY SYSTEM

History

A thorough family history is imperative for all infants suspected of having a urogenital abnormality. Many urogenital problems have an inheritance pattern, suggesting a genetic predisposition. The history should focus on family members who have had a renal transplant or have undergone dialysis, those with a history of renal failure, and those with cystic kidney disease or anomalies of the GU system. A review of family history should also include fetal or neonatal deaths and the presence of individuals with external genitalia abnormalities, such as hypospadias, ambiguous genitalia, or undescended testicles. The prenatal history should be reviewed for antepartal factors associated with renal abnormalities, including oligohydramnios, an abnormal prenatal ultrasound, or perinatal depression.

The neonatal history should include the following questions:

1. Has the infant urinated, and, if so, how long following delivery? Normal voiding occurs within the first 24 hours of life. Care should be taken to note whether the infant voided in the delivery room.
2. Has the infant undergone any significant hypoxic episodes that may result in decreased renal blood flow?
3. Is the fluid intake sufficient relative to the infant's clinical status, gestational age, and immediate environment (radiant warmer or humidified isolette)? A radiant warmer can increase insensible water losses, thereby increasing fluid requirements.
4. Is the infant under treatment for jaundice? (Phototherapy can increase insensible water losses.)
5. Is the infant experiencing any bleeding or increased gastrointestinal losses from nasogastric suctioning, vomiting, diarrhea, or increased ostomy output?
6. What is the specific gravity of urine? (Normal range is 1.003–1.015.)
7. What is the infant's gestational and chronological age?
8. Has the infant received any nephrotoxic medications?
9. What is the infant's blood pressure? (Hypotension can indicate volume depletion, whereas hypertension [HTN] may be associated with an underlying renal abnormality.)

PHYSICAL ASSESSMENT

Physical examination should include inspection, palpation, and percussion. Auscultation is generally not useful in assessment of the renal system.

Inspection

Observation of the abdominal region is essential in infants suspected of having renal abnormalities. One should note the presence of abdominal distention, including whether the distention is localized to one side or is generalized. Any abdominal asymmetry is considered an abnormal finding. The presence of bladder distention should also be noted. Although mild abdominal

protuberance in the neonate may be normal due to the relative weakness of the abdominal musculature compared to infants who are several months older, an absence of muscle tone is characteristic of prune-belly syndrome. The umbilicus should be assessed for hernias and/or drainage. If possible, the urinary stream should be assessed. A continuous, straight stream is considered normal.

The genital and perineal area should be carefully inspected. Peritoneal tissue leading to the anal opening should be intact and smooth in appearance. Any abnormal openings, depressions, or swellings should be noted. The anus is normally located midline and can be tested for patency by gentle insertion of a gloved, well-lubricated small finger. Gentle stroking of the anal tissue and observation for anal sphincter constriction tests the anal wink, indicating adequate muscle tone.

Male infants require inspection of the skin covering the scrotum for color and the presence of rugae, edema, or ecchymosis. If the infant is full term, the scrotal sac should be full, and rugae should be present. The premature male infant exhibits a generally flaccid, smooth scrotal sac. The scrotum is generally darkly pigmented, without bluish discoloration that could denote disruption of circulation to the area, indicating the possible presence of a testicular torsion. An enlarged or edematous scrotum may accompany a hydrocele (a trapping of fluid in the tunica vaginalis) or may result from pressure during the birth process, especially during a breech delivery. If a hydrocele is suspected, transillumination of the scrotum with a good light source, such as a transilluminator or a flashlight, helps determine the presence of fluid. When transilluminated, fluid will allow light to pass through what appears as a highly lightened area.

Penile size, resting position, and position of the urinary meatus should also be assessed. An abnormally large or small penis may indicate a genital abnormality. A micropenis is suspected when the penis measures less than 2 to 2.5 cm in length and can be associated with renal, genital, and chromosomal abnormalities. Priapism, or a constantly erect penis, is also an abnormal finding. The urinary meatus should be located midline on the ventral portion of the glans penis. Dorsal or ventral placement of the meatus can occur anywhere along the shaft of the penis and is considered abnormal. A urinary meatus located on the dorsum of the penis is known as an epispadias and a hypospadias if the opening is displaced along the ventral penile surface. A hypospadias can be associated with a downward curvation, bowing, or chordee of the penis. The foreskin of the uncircumcised male may be gently retracted for accurate observation of meatal location and then returned to its unretracted state to avoid swelling and possible decreased penile circulation.

Female infants require inspection of the labia, clitoris, urinary meatus, and external vaginal orifice. The labia minora in the term infant should be well formed, and the labia majora should be present and extend beyond the labia minora. As gestational age decreases, the labia majora is smaller, and in premature infants, the labia minora may be larger than the labia majora. The labia may be darkly pigmented and is of no clinical significance. Because the labia may not be fully developed in premature infants, the clitoris in infants born preterm may appear prominent but, if normally sized, is considered normal. The urinary meatus should be patent and anterior to the vaginal orifice. The vagina should be inspected for patency, and any vaginal secretions should be noted. A white, milky vaginal secretion in the first few days of life, followed by pseudomenses or slight vaginal bleeding, is a normal finding. A hymenal tag may be present, usually disappearing within the first few weeks, and is considered a normal finding.

In both male and females, bruising and swelling of the genitalia may occur following a breech delivery. Ecchymosis and sometimes hematomas may also occur after traumatic delivery. These birth-related findings are transient and can be expected to resolve within several days. The inguinal areas should be assessed for the presence of an inguinal hernia. The genital and peritoneal regions must be observed to ensure that there is a clear differentiation of the sexes. If not, ambiguous genitalia must be considered (see Chapter 10, Endocrine System).

Palpitation

This portion of the physical examination may be stressful to the infant and thus is best left until the end of the examination. Place the infant in the supine position with the knees and hips flexed and provide a means of non-nutritive sucking for the infant. This position generally places the infant at ease and facilitates relaxation of the abdominal muscles. The abdomen is then gently palpated with a gradual downward movement, anteriorly to posteriorly. To palpate the kidneys, place the fingers of one hand along the flank, while the thumb palpates the abdomen. This allows the examiner to trap the kidney's pole between the fingers and the thumb (ballottement). Deep palpitation is required to manually assess the kidneys and is, therefore, reserved only for infants suspected of having a GU or renal abnormality. The kidneys are only reliably palpated in the first 1 to 2 days of life (Tappero & Honeyfield, 2019).

In males, palpate the scrotal sac for each testis and cord. If the testis is absent, palpate along the canal to assess its location. The scrotal sac may be palpated by gently pressing the tissue between two fingers, one on the anterior surface and the other on the posterior surface. Gentle movement of the fingers upward over the scrotum until the testes are detected bilaterally indicates whether one or both testes are descended and their location in relationship to the internal ring in the inguinal canal. Until 28 weeks' gestation, the testes are abdominal organs, and between 28 and 30 weeks, they begin to descend into the inguinal canal. The cremasteric reflex, recoil of the testes toward the inguinal canal, may be elicited by gentle stroking of the upper thigh or scrotal sac.

Percussion

If bladder distention is palpated or observed, percussion should be performed. This technique is useful in determining whether the area is fluid filled or a solid mass. If the bladder is filled with fluid, percussion will invoke a somewhat tympanic sound, while a dull sound will be noted if the mass is solid. Percussion may also be used over the entire abdominal region. Examination of the abdomen and gastrointestinal system is discussed in depth in Chapter 8, Gastrointestinal System.

Related Findings

All infants should be inspected for general characteristics suggesting renal abnormalities. Severe oligohydramnios sequence facies (flattened, beaklike nose; wide-set eyes; micrognathia; disproportionately large ears; and short neck) accompanied by abnormal positioning of the hands and feet and pulmonary hypoplasia are associated with oligohydramnios and may indicate the presence of a renal disorder. Since genetic syndromes commonly have associated renal abnormalities, one should assess for characteristics consistent with the presence of genetic abnormalities. A single umbilical artery is present in up to 1% of newborns (Luo et al., 2017). **Quality and Safety:** **Historically, the presence of a single umbilical artery was thought to be strongly associated with renal abnormalities, and therefore, a renal ultrasound was recommended. Recent evidence has suggested that the association is not as strong as previously thought and that an ultrasound may only be indicated in infants with other symptoms of renal disease** (de Boom et al., 2010). The ears should be assessed for

TABLE 18.1

SYNDROMES ASSOCIATED WITH THE DEVELOPMENT OF UROGENITAL DISORDERS

Syndromes	Renal Component	Genital Component
Severe oligohydramnios sequence	Renal agenesis	Absence of vas deferens, seminal vesicle, upper vagina, uterus
Meckel's syndrome	Polycystic kidneys	Ambiguous genitalia Hypoplastic phallus Cryptorchidism
Trisomy 21	Cystic kidneys and other renal anomalies	Hypoplastic penis and scrotum Cryptorchidism
Trisomy 18	Dysplastic renal system	Hypoplastic clitoris and labia minora Cryptorchidism
Turner's syndrome	Horseshoe kidney	Infantile genitalia Duplications of the collecting system
Prune-belly syndrome Urinary tract dysplasia	Bladder and ureter dilation	Patent urachus Cryptorchidism
Errors of metabolism	Renal tubular dysfunction	Galactosemia Tyrosinemia Glycogen storage (von Gierke's) disease
Adrenogenital syndrome	Masculinization of the female clitoral hypertrophy	Incomplete masculinization of the male Hypospadias Hypoplastic penis Cryptorchidism

abnormalities since preauricular tags have been associated with urinary tract abnormalities. Meningomyelocele and other neural tube defects may cause decreased or absent bladder innervation, resulting in a neurogenic bladder and bladder distention. If untreated, the associated urinary stasis may result in a urinary tract infection (UTI). Syndromes associated with renal and genital problems are listed in Table 18.1.

Urine Collection

Urine collection is a relatively simple procedure in the neonate, and several adhesive-backed collection bags are currently available. When placing urine collection bags, care should be taken to not include the rectum or the scrotum within the opening of the bag. The penis should not be left in urine because infection and skin irritation may occur. To avoid skin irritation when using adhesive-backed collection bags, care should be taken to maintain skin integrity. Alternative collection systems can be used if accurate measurement of urine output is not needed. Cotton balls can be placed inside diapers to catch a small specimen for dipstick analysis or for measurement of specific gravity. Many institutions now use super absorbent disposable diapers, which can potentially alter the result of urine tests. Nursing research is needed to evaluate the accuracy of specific laboratory tests when using these newer products.

When sterile urine specimens are required for culture, a suprapubic bladder tap or urethral catheterization must be performed. Performance of a suprapubic tap requires minimal equipment and time. The lower abdomen is prepared with an antimicrobial solution and allowed to dry. If the infant has voided within the previous hour, the attempt should be delayed until the infant's bladder is full. If severe dehydration, abdominal congenital anomalies, inguinal hernias, or distention are present, a suprapubic tap may be contraindicated. Nonpharmacological and/or pharmacological pain relief should be provided. The procedure is usually performed with a 3-mL syringe and a 23- to 25-gauge straight needle. The needle is placed midline, 1 to 1.5 cm above the symphysis pubis, and is inserted perpendicularly or at a slight angle, pointing toward the head. Entry into the bladder is determined when resistance decreases as the needle is inserted. A slight traction on the plunger facilitates aspiration of urine into the syringe. If no urine is obtained on the first attempt, a second attempt should be delayed until sufficient urine buildup has occurred. At the completion of the procedure, pressure should be applied over the puncture site until all evidence of bleeding has ceased.

Emergency Alert: Suprapubic aspiration can result in complications, including uterine and bowel perforation, trauma to other portions of the renal system, and infection. The procedure is not recommended for neonates with clotting disorders or disseminated intravascular coagulation. Urethral catheterization may also be performed to obtain sterile urine specimens. After prepping the area with an antimicrobial solution, a 3.5- or 5-French feeding tube or urinary catheter is coated with lubricant and inserted into the urethra until urine returns. Discarding the initial 1 to 2 mL of urine obtained may increase the accuracy of the culture results. Because bagged specimens have a significant risk of contamination, they are not recommended for Gram stain or culture.

Urinalysis

One of the first steps in a urogenital workup is a urinalysis. Variables normally assessed in a urinalysis include color, pH, specific gravity, white blood cells, blood, and protein. Urinalysis includes gross assessment as well as dipstick and microscopic evaluation. The urine is most often straw colored, but this may be altered by the type and amount of solutes. Dipstick testing of urine can provide a wide range of information. This test requires that one to two drops of urine be placed on the dipstick, or the stick may be dipped into a specimen of urine. The results are generally obtained within 30 seconds to 1 minute; however, the exact timing required is based on the manufacturer's suggested procedure and can be found in either the instruction manual or on the dipstick bottle itself. In addition to pH, specific gravity, protein, and blood, the dipstick test may also assess the presence of leukocytes, nitrites, glucose, bilirubin, and ketones in the urine. The presence of leukocytes and nitrites can be indicative of a UTI.

Renal regulation of acid–base balance has previously been discussed. Urinary pH values range from 4.5 to 8 and reflect the kidney's attempt to maintain acid–base balance. The newborn initially excretes alkalotic urine with a pH of approximately 6. Urine pH values in the newborn should be evaluated in relation to the serum bicarbonate values. Production of alkaline urine with documented metabolic acidosis may indicate renal pathology.

Specific gravity indicates the kidney's ability to concentrate and dilute urine, and normal levels typically range from 1.001 to 1.015. Since infants have a decreased ability to concentrate urine, specific gravity measurement in the newborn can be misleading. High specific gravities can be an indication of either dehydration or high solute excretion. Excretion of glucose and protein in the urine may artificially increase the specific gravity in the newborn. Urine osmolality or the number of solute particles dissolved in a given volume of solution is a more accurate measure.

Urine Chemistries

Urine chemistries can be helpful in determining fluid and electrolyte balance when evaluated in comparison to serum electrolyte levels. Sodium excretion is very high in the fetus and premature infant but tends to decrease with increasing gestational age. While the term infant conserves renal sodium and renal sodium loss is small, sodium loss in the premature infant can be very high, necessitating correction in intravascular fluids or feedings. The increased sodium loss in premature infants is related to an impaired reabsorption of sodium in the renal tubules as well as unresponsiveness to aldosterone.

Potassium is freely filtered by the glomerulus, but urinary potassium levels are low because the majority of filtered potassium is reabsorbed by the proximal tubule and, to a lesser extent, the loop of Henle. Urinary potassium levels reflect the amount secreted by the collecting tubule. As a result, increased potassium load can significantly increase serum potassium levels. Hyperkalemia can be a life-threatening situation and is defined as a potassium level greater than 6 mEq/L. Infants who are extremely low birth weight (<1,000 g) are at a higher risk of hyperkalemia due to a reduced GFR, acidosis, and an immature tubular response to aldosterone.

Blood Urea Nitrogen and Creatinine

Evaluation of blood urea nitrogen (BUN) and creatinine levels is essential when assessing renal function. Creatinine is a breakdown product of creatinine phosphate in the muscles. It is freely filtered by the glomerulus, and creatinine levels are the most common indicator of GFR (Boer, de Rijke, Hop, Carnsberg, & Dorresteijn, 2010). Creatinine levels at birth are relatively high and reflect maternal levels, gestational age, and the infant's GFR. The level may temporarily increase on day 1, but then begins to decrease over the first few weeks of life (Boer et al., 2010). The more immature the infant, the higher the initial creatinine level and the longer it takes to reach normal levels. Serial levels are necessary to accurately evaluate renal function. Although these indices are not absolute indicators of long-term renal dysfunction, they can be used to identify and treat acute problems. During the first few days of life, BUN levels should not be greater than 20 mg/dL. Elevated BUN levels can result from significant dehydration, ingestion of high-protein loads, and renal dysfunction. Table 18.2 provides a summary of blood and urine chemistries in both term and preterm infants.

Urine Culture

Urine culture in the newborn is used to assess for UTI. UTIs are common in the infant and can occur in association with urinary tract deformities, due to sepsis, or when organisms have been introduced via invasive procedures. Either in-and-out catheterization or suprapubic tap to maintain the sterility of the specimen should be used to obtain urine cultures.

RADIOLOGICAL EVALUATION

Radiological examination includes a variety of tests available for determining anatomic and physiological function.

TABLE 18.2

DIFFERENCES IN RENAL FUNCTION BETWEEN FULL-TERM AND PRETERM INFANTS

	Preterm	Full-Term
Creatinine clearance 1 week after birth (mL/minute/1.73 m^2)	11 ± 5 (GA 25–28 weeks) 15 ± 6 (GA 29–34 weeks)	46 ± 15
Plasma creatinine 1 week after birth (mg/dL)	1.4 ± 0.8 (GA 25–28 weeks)	0.5 ± 0.1
Maximum urine osmolality (mOsm/kg H_2O)	400–700	600–900
Proteinuria (mg/m^2/day)	86–377	68–309
Plasma bicarbonate (mEq/L)	19.5 ± 2.9	21.0 ± 1.8
Mean fractional excretion of sodium (%)	4 (GA ≤30 weeks)	≤2

GA, gestational age.

Source: Modified from Springate, J. E., Fildes, R. D., & Feld, L. G. (1987). Assessment of renal function in newborn infants. *Pediatrics in Review, 9*(2), 51–56. doi:10.1542/pir.9-2-51

Renal Ultrasonography

One of the safest and most useful tests to evaluate for the presence of renal anomalies is ultrasonography. Ultrasound is readily available, is noninvasive and inexpensive, and can detect most structural renal abnormalities. The two-dimensional mode and Doppler imaging are the usual techniques. The two-dimensional mode may be used to determine kidney structure, and Doppler imaging provides information relative to blood flow in the renal arteries and veins. Ultrasonography is useful in identifying renal obstruction, hydronephrosis, the presence of renal calculi, and, in some cases, advanced parenchymal disease.

Prenatal Ultrasound

Currently, the majority of pregnant women undergo prenatal ultrasounds between 16 and 20 weeks' gestation. Seventy percent of renal and urinary tract anomalies are diagnosed during prenatal ultrasound (Dias et al., 2014). Prenatal ultrasound is proficient in providing information regarding amniotic fluid volume, degree of urinary tract obstruction, as well as the presence of hydronephrosis. The presence of abnormally sized kidneys, renal cysts, hydronephrosis, abnormal bladder size, and oligohydramnios suggests significant renal or urinary tract abnormality. Amniotic fluid is predominantly produced by the kidneys, and anhydramnios or severe oligohydramnios may be indicative of severe kidney disease (Dias et al., 2014). Normal amniotic fluid levels are critical for normal lung development, and severe oligohydramnios can result in pulmonary hypoplasia.

Prenatal diagnosis of renal abnormalities provides an opportunity for family counseling and, if necessary, allows the family time

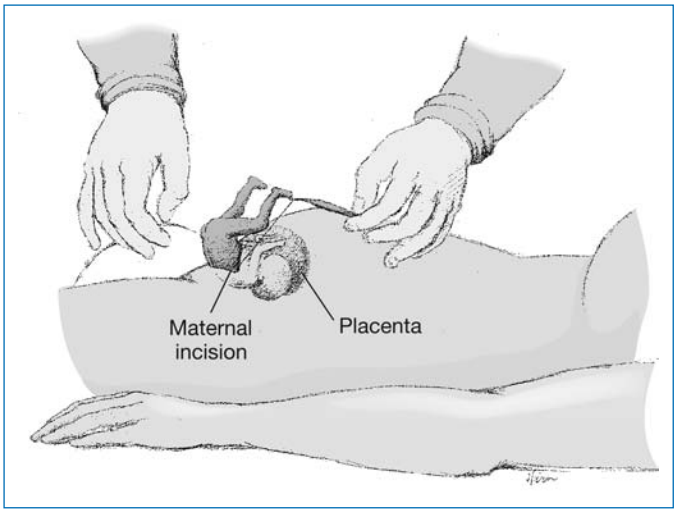

FIGURE 18.4 Fetal surgery to prevent hydronephrosis.

to make treatment decisions, including elective termination if the anomaly is incompatible with life. It also allows maternal transfer prior to a tertiary care center so that the infant can be provided optimal care in the delivery room and immediately following delivery. Because of prenatal diagnosis, treatment of neonatal renal disease may be initiated prior to the onset of symptoms, potentially improving long-term prognosis. Prenatal diagnosis of renal abnormalities can cause significant family stress, and families require honest, accurate information. To become a source of this information, nurses require an understanding of the disease process and treatment options for renal abnormalities.

Prenatal ultrasound also provides an opportunity for in utero treatment of certain disorders. Placement of a vesicoamniotic shunt (a shunt placed in the bladder to drain urine into the amniotic fluid) can be used to increase amniotic fluid volume and reduce the complications of oligohydramnios (Figure 18.4; Clayton & Brock, 2018). The goals of in utero shunting include restoration of adequate amniotic fluid volume for lung development and preservation of renal function by relieving obstruction. This procedure is associated with varied success, and complications include dislodgement, premature labor, urinary ascites, and chorioamnionitis (R. K. Morris et al., 2015; Nassr et al., 2017).

Voiding Cystourethrogram

During a voiding cystourethrogram (VCUG), a urinary catheter is placed into the bladder, contrast material is instilled, and fluoroscopy is then used to monitor bladder filling and voiding mechanisms and to assess for the presence of vesicoureteral reflux (VUR; Choi, Cheon, Kim, & Kim, 2016). VCUGs are primarily used to assess for the presence of VUR but can also assess bladder and urethral function and anatomy.

Renal Scintigraphy With Dimercaptosuccinic Acid Scan

This test is considered the gold standard for assessment of renal parenchyma and is usually performed to evaluate renal function and assess for renal damage. It involves intravenous (IV) administration of an actively labeled substance (radioisotope) radioactive isotope. The most commonly used radioisotope is technetium-99m mercaptoacetyltriglycine (^{99m}Tc-MAG-3). The radioactive isotope is taken up by the renal parenchyma to identify regions of decreased update representing inflammation or renal scarring. It can also be used to visualize kidney mass as well as ureter and bladder outline. In the premature infant, contrast material should only be used when absolutely necessary, since the hyperosmolarity of the solution can lead to further renal compromise.

Diuretic Renography

A diuretic renography is another radionuclide test that is used to differentiate between obstructive and nonobstructive uropathies and to assess renal function. A radioisotope injection is administered, followed 15 to 30 minutes later by a diuretic injection. The diuretic facilitates the movement of the radioisotope through the renal system, and a gamma computer tracks the isotope's movement. If urinary obstruction is present, the isotope's progress is slowed or impeded and is shown as retention of the radioactive substance. If dilation exists along the renal system, urine is retained at the ureteropelvic junction (UPJ) until overflow occurs with diuretic action. Stretching of the muscle fibers at this point causes strong contractions, release of urine, and rapid movement of the isotope with a sharp, immediate decline in isotope concentration. In a normal kidney, the isotope takes about 25 minutes to clear the system.

Computed Tomography and Magnetic Resonance Imaging

Computed tomography (CT) and magnetic resonance imaging (MRI) provide high-resolution cross-sectional imaging and may be useful to provide additional information in the setting of complex urological abnormalities (Garcia-Roig, Grattan-Smith, Arlen, Smith, & Kirsch, 2016). In addition, fetal MRI is becoming more accepted as a way to more precisely characterize GU abnormalities prior to birth (Tubre & Gatti, 2015).

MANAGEMENT

Fluid, Electrolytes, and Nutrition

When renal failure is suspected, serum electrolytes, phosphorus, and calcium levels should be monitored as frequently as clinically indicated to prevent derangement. Fluids should be carefully managed relative to the clinical presentation and response to therapy.

Abnormalities in fluid status, including both dehydration and overhydration, are common and must be carefully monitored. Nursing management involves the ongoing assessment and reporting of signs and symptoms consistent with abnormalities in hydration. Daily or twice-daily weights may be required for determination of excessive fluid retention or loss. Accurate intake and output must be measured, and urine specific gravity should be frequently monitored. The presence of edema due to fluid overload can be assessed by observing for the presence of periorbital edema and edema of the hands, feet, labia, and scrotum. Pitting should be determined by gentle depression of a fingertip into the suspected edematous site.

Hyponatremia is common and is usually related to fluid overload and increased antidiuretic hormone (ADH) production (Jetton & Sorenson, 2017). A sodium level less than 120 mEq/L can result in seizures and must be treated with sodium replacement therapy. **Quality and Safety: Careful monitoring of fluid status and restricting fluid intake to insensible water loss plus urinary output is imperative to prevent hyponatremia in infants with severe oliguria.**

Due to oliguria or anuria, hyperkalemia is also a potential complication of renal failure, and maintenance of appropriate potassium levels is imperative.

Emergency Alert: If hyperkalemia is associated with ECG changes, it may result in a medical emergency; careful cardiac monitoring is essential to detect any abnormal rhythms or patterns resulting from alterations in potassium levels (Bonilla-Felix, 2017).

Potassium should not be added to parenteral fluids until an appropriate urine output has been established. The goals of hyperkalemia management are to decrease myocardial excitability, enhance cellular potassium uptake, and facilitate potassium excretion. Administration of IV calcium gluconate aids in decreasing myocardial excitability. Cellular uptake of potassium can often be achieved through combined administration of glucose and insulin as well as administration of sodium bicarbonate alone (1 mEq/kg). These measures are the only temporary solutions to the problem since they do not remove the excess potassium from the body. Exchange transfusions and administration of Kayexalate can facilitate potassium excretion. The administration of a cation-exchange resin, such as Kayexalate, binds the serum potassium and actively removes it from the body (Bonilla-Felix, 2017). Each gram per kilogram administered will decrease the potassium level by 1 mEq/L. Since the mechanism of action is exchange of a sodium ion for a potassium ion, hypernatremia, fluid overload, and congestive heart failure are potential side effects of Kayexalate. Administration of Kayexalate is not an immediate solution for hyperkalemia since it takes several hours to take effect. If the hyperkalemia is severe or if conventional therapies are unsuccessful, dialysis may be necessary.

Because of decreased excretion, hyperphosphatemia may also occur with renal disease, causing severe hypocalcemia and even tetany. Aluminum hydroxide is a treatment option by binding phosphorus in the intestines, but dialysis is often indicated for treatment of severe hyperphosphatemia. A low-phosphorus formula such as Similac PM 60/40 (Ross Laboratories, Columbus, OH) or spinal muscle atrophy (SMA; Wyeth, Madison, NJ) may be indicated in infants receiving enteral nutrition.

Hypocalcemia is common and, if symptomatic, can be treated with calcium supplements. Close nursing observation is necessary during IV administration since rapid administration can precipitate cardiac arrest. Vitamin D supplementation is a useful adjunct for correction of calcium levels through facilitation of intestinal calcium absorption during enteral feedings. Metabolic acidosis often occurs in conjunction with renal disease due to decreased secretion and increased production of hydrogen ions. Sodium bicarbonate is indicated if the pH falls to less than 7.2.

Growth and nutrition may be compromised due to the necessary fluid and protein restriction necessitating meticulous attention to nutrition and fluid status. A positive nutritional status positively affects both the short- and long-term outcomes of infants with renal disorders. If fluid restriction is necessary, attempts should be made to increase the total caloric consumption without increasing the overall fluid volume. The overall goal of nutritional therapy is to preserve a positive nitrogen balance while avoiding increases in nitrogenous waste products and increased BUN levels. Protein intake should be determined by overall caloric intake and BUN levels, and recommendations usually include 1 to 2 g/kg/day (Zaritsky & Warady, 2014).

Skin Management

Impaired skin integrity is common, especially in the presence of severe edema. The infant's position should be changed every 2 hours to decrease the effects of dependent edema and to improve circulation. The skin around any operative site should be inspected with every dressing change for signs of irritation or infection and should be kept clean and dry to prevent skin breakdown and infection.

Respiratory Management

Due to oligohydramnios, respiratory compromise is common in infants with alterations in urinary elimination. During fetal life, insufficient amniotic fluid is linked to decreased development of the respiratory tree (see discussion on severe oligohydramnios sequence's syndrome). Varying degrees of lung hypoplasia may exist, resulting in potentially significant respiratory distress.

Before extensive therapy is initiated for the treatment of renal anomalies, careful evaluation of respiratory status should be performed (see Chapter 6, Respiratory System). Measures to improve renal function may not be considered if respiratory capacity is insufficient to support life.

General Preoperative Management

If surgical intervention is indicated, preoperative care is directed toward achieving and maintaining fluid and electrolyte balance and ensuring hemodynamic stability. Ongoing assessment for signs of a UTI, including poor feeding, temperature instability, cyanosis, and other subtle signs of infection, is necessary. Surgery should be delayed until the infant is free from any possible infection including UTIs.

General Postoperative Management

Postoperatively, nursing management is again focused on careful assessment and monitoring of fluid and electrolyte status as well as the hemodynamic system. Vital signs including blood pressure, pulse, and respiration should be monitored every 2 to 4 hours after the initial post-op period. Accurate measurement of fluid intake and output is critical. Dressings should be inspected for bloody drainage or secretions. Initially, a small amount of bleeding at the site is common, but prolonged or heavy bleeding should be reported to the medical team. Depending on the overall clinical status of the infant, feedings can usually be resumed once bowel sounds can be auscultated and the nasogastric tube has been removed.

If renal function is at risk due to a blockage at the level of the ureter, surgical placement of a nephrostomy tube may be indicated (Hwang et al., 2018). Generally, nephrostomy tubes are considered only for severe bilateral obstruction with renal failure or if there is evidence of renal insufficiency in a severely obstructed unilateral kidney (Lang, Allaei, Robinson, Reid, & Zinn, 2015). Because the renal system is highly vascularized, the chance of bleeding and infection is increased. After insertion of a nephrostomy tube, pink-tinged urine or even urine with visible bloody streaks is common. Because they are located within the renal pelvis, these tubes should not be irrigated. The tubes should be connected to a closed drainage system to maintain sterility, and a clean dressing surrounding the tube should be used to maintain the position and to protect the underlying skin. Upon removal, leakage of urine at the site for up to 48 hours is considered normal.

Parental Support

Parental response to a critically ill infant will vary and must be addressed individually. Consenting to a major surgical procedure on their infant so early in life may be very difficult. The parents must be given accurate information regarding their infant's prognosis and should be encouraged to express their concerns. Use of an interdisciplinary team is essential. Collaboration among the neonatologist, pediatric urologist, nurse, clergy, and social worker will help parents adjust to this frightening situation. If the infant's clinical status is terminal, early identification and involvement of their support network, including family, friends, and clergy, can assist the parents in coping with the reality that their child may not survive. In order for the family's needs to be met, the bedside nurse must anticipate their needs and respond appropriately (Purdy, Craig, & Zeanah, 2015).

The general principles of collaborative management have been outlined. The remainder of the chapter addresses the most common GU neonatal problems.

URINARY TRACT INFECTIONS

Pathophysiology

UTIs are common in infants and are defined as infection of the kidney and/or the bladder. Infection occurring in the kidney is called pyelonephritis, whereas infection of the bladder is cystitis. The presence of a UTI results in acute morbidity in the neonatal population and, if not properly treated, can result in long-term sequelae, including decreased renal function, renal scarring, and HTN. The presence of a UTI can also be a sign of an underlying renal abnormality (Arshad & Seed, 2015).

Risk Factors

The incidence of UTIs is 7% to 15% in infants less than 30 days old, and the risk is even higher in infants born premature or who are critically ill (Bonadio & Maida, 2014). UTIs are more common in male infants, potentially due to an increased risk of UTI in uncircumcised males (B. J. Morris & Wiswell, 2013). Traditionally, it was thought that UTIs were strongly associated with the presence of VUR, but recent evidence has refuted this assumption. The risk of a UTI is increased in infants with a neurogenic bladder that is associated with neural tube defects, including meningomyelocele, and occurs when the bladder lacks innervation and, therefore, fails to completely empty.

Clinical Manifestations

During the first 1 to 2 months of life, clinical manifestations of UTIs are often nonspecific and subtle and include temperature instability, poor feeding, cyanosis, abdominal distention, poor weight gain, hepatomegaly, jaundice, and fever (Arshad & Seed, 2015). A urine dipstick is often positive for protein, blood, nitrites, or leukocytes (Joseph & Gattineni, 2016). The presence of a UTI may also be discovered during a general sepsis evaluation.

Diagnosis

Initial examination of the infant suspected of having a UTI includes a thorough family and perinatal history. Any positive familial history of pyelonephritis or nephritis as well as maternal infections should be noted. Neonatal procedures, including suprapubic bladder taps and bladder catheterization, should be noted along with the dates these procedures were performed in order to estimate the incubation time for possible infection. Infants with signs of a UTI may have nonspecific inflammatory markers, including an elevated or decreased white blood cell count, a left shift on complete band count, and an elevated C-reactive protein (CRP). A urinalysis or dipstick positive for either leukocytes or nitrites should be considered evidence of a UTI until urine culture results are obtained. The presence of protein and blood in the urine suggests a UTI but is not conclusive.

A urine Gram stain and culture should be obtained using either suprapubic aspiration or sterile bladder catheterization. Bagged urine specimens should never be used for culture purposes due to the high likelihood of contamination (Roberts et al., 2011). False-positive culture results obtained from bagged specimens can lead to misdiagnosis and inappropriate treatment. Any bacteria obtained from a suprapubic aspiration must be considered diagnostic, whereas urine obtained via catheterization can have up to 10^5 CFUs (colony-forming units) before a UTI is diagnosed. Because of the strong possibility of systemic infection, a blood culture should also be obtained. All Gram stains and cultures should be obtained prior to the initiation of antibiotic therapy, allowing appropriate diagnosis and identification of pathogens (Roberts et al., 2011).

Prognosis

With prompt diagnosis and treatment, the prognosis is generally excellent for isolated UTIs. If left untreated, the potential for serious complications, including severe damage to the renal system, exists, including renal scarring, decreased renal function, and HTN (Stein et al., 2015). The prognosis of infants with underlying renal abnormalities is dependent on the severity and type of abnormality.

Collaborative Management

Prompt treatment is imperative to prevent complications, including renal scarring, which can lead to HTN or permanent kidney failure. Empiric broad-spectrum IV antibiotic therapy should be initiated following completion of the diagnostic workup and continued for 7 to 14 days IV (Roberts et al., 2011). Following identification of the infective organism on culture and specification of sensitivities, antibiotic coverage may be adjusted. A repeat urine culture should be obtained 48 to 72 hours following initiation of treatment. The majority of UTIs are caused by *Escherichia coli*; however, *Klebsiella*, *Pseudomonas*, *Proteus*, *Enterococcus*, *Staphylococcus*, and *Candida* are becoming more common as causative agents in the NICU (Arshad & Seed, 2015). UTIs commonly occur in conjunction with systemic sepsis, and it may be difficult to determine whether the UTI is a result of sepsis or is the underlying cause.

Historically, infants diagnosed with a UTI underwent a VCUG to assess for VUR because of a presumed association between VUR and UTIs. Evidence now exists that the risk of recurrent UTI is not significantly affected by VUR, and the American Academy of Pediatrics (AAP) currently recommends that a VCUG not be performed following the first UTI unless the renal ultrasound indicates the presence of abnormalities, including hydronephrosis, renal scarring, severe VUR, or obstructive uropathy (Flannery et al., 2017; Roberts et al., 2011). A VCUG is also indicated if the infant is affected by subsequent UTIs. A renal ultrasound is recommended following all UTIs. It is a safe and easy procedure that may provide important information regarding an underlying renal abnormality (Roberts et al., 2011). Controversy exists concerning the necessity of prescribing prophylactic antibiotic therapy to all infants until the presence of reflux has been eliminated. Prophylactic antibiotics do not completely prevent future UTIs or the scarring associated with reflux, and the risk of subsequent UTIs is not increased without prophylactic antibiotics (Roberts et al., 2011).

Nursing Management

Nurses play a key role in monitoring infants in the NICU for symptoms of UTIs. When an infant exhibits symptoms or has other signs including the presence of leukocytes, nitrites, blood, or protein in the urine, these should be reported to the medical team for further evaluation. If a VCUG is performed, it is important for nurses to appreciate that this procedure may be uncomfortable to the infant and stressful to the family. Nonpharmacological interventions, such as sucrose nipples, swaddling, and non-nutritive sucking, should be provided, and while pharmacological pain interventions are rarely required, they should be administered if the infant's pain scores are elevated. Discharge instructions for infants who have been diagnosed with a UTI should include signs and symptoms of a UTI, and parents should be instructed to seek medical care immediately if symptoms occur (Roberts et al., 2011).

CIRCUMCISION

Circumcision is removal of the prepuce from the glans of the penis. Although the function of the prepuce is not entirely understood, it is probably involved in protection of the glans. Circumcision is

one of the most commonly performed procedures in the United States, and approximately 89% of neonates are circumcised (Introcaso, Xu, Kilmarx, Zaidi, & Markowitz, 2013). There are currently three commonly utilized methods of circumcision: the Gomco clamp, the Plastibell device, and the Mogen clamp. The method utilized is generally dependent on individual preference and familiarity.

Until 1989, the AAP recommended against routine circumcision based on lack of medical indication for the procedure. In 1989, a multidisciplinary Task Force on Circumcision established by the AAP summarized the pros and cons of circumcision but did not make a specific recommendation regarding the necessity of routine circumcision (Schoen et al., 1989). In 1999, this same task force again summarized the existing scientific evidence, stating that although potential benefits to circumcision existed, there were insufficient data to recommend routine circumcision. They recommended that parents be provided with accurate and unbiased information and allowed to make the decision whether or not to circumcise their child (Lannon et al., 2012). The World Health Organization (WHO) takes a more proactive stance, stating that circumcision should be considered an effective intervention of HIV prevention in areas with heterosexual HIV epidemics and a low rate of male circumcision (WHO, n.d.).

Males who are not circumcised as neonates are at increased risk of infection of the prepuce (posthitis) or glans (balanitis) or both (balanoposthitis) and obstruction of the urethra (phimosis; B. J. Morris et al., 2017). Uncircumcised infants have a 9.9 times higher risk of UTI, and the lifetime UTI incidence increases from 8.8% to 32.1% in uncircumcised males (B. J. Morris & Wiswell, 2013). This increased risk is thought to be due to the higher periurethral colonization of bacteria in uncircumcised males that can be introduced into the urethral opening.

Circumcision is also associated with long-term benefits, including a decreased risk of HIV, and in the United States, it is estimated that routine neonatal circumcision would decrease the rate by 2,500/year (Lei et al., 2015; Nelson, 2015; Sharma et al., 2018). In addition, the risk of human papillomavirus may be decreased by 43% (Albero, Castellsague, Giuliano, & Bosch, 2012). Circumcision has also been associated with a reduced risk of penile cancer, probably due to a decrease in the incidence of phimosis (Larke, Thomas, dos Santos Silva, & Weiss, 2011). However, the American Cancer Society states that due to the low risk of penile cancer among uncircumcised males in the United States, circumcision should not be recommended only to prevent penile cancer (American Cancer Society, 2017).

Complications of circumcision are rare, occurring in less than 5% of cases (El Bcheraoui et al., 2014). Most complications are minor and include bleeding, pain, inadequate skin removal, and mild infection. Bleeding is by far the most common complication, occurring in 1% of infants undergoing circumcision (Krill, Palmer, & Palmer, 2011). A hematological workup is warranted in patients who have persistent or significant bleeding associated with the procedure. More serious complications, including amputation of the glans, glandular necrosis, and meatal stenosis, are rare (Krill et al., 2011). Complications occur most often when the wrong-sized equipment is used or when the clinician performing the procedure is inexperienced or untrained. Although the complication rate of circumcision is higher in older individuals, some suggest that parents are providing consent for what may be considered a nonessential procedure and perhaps the procedure should be delayed until the child reaches adolescence and can make an independent and informed decision.

It is well known that performing circumcision without analgesia produces significant pain and physiological stress, underscoring the need for appropriate procedural analgesia, which is recommended by the AAP. The use of a dorsal penile nerve block, a ring block, and eutectic mixture of local anesthetics (EMLA) have all been shown to decrease the pain associated with circumcision, with the dorsal penile nerve block being found most effective in pain control (O'Conner-Von & Turner, 2013). Effective adjuncts to nerve blocks include non-nutritive sucking, sucrose nipples, and padded chairs; these therapies should be provided in addition to more invasive pain relief.

Nursing Management

Nursing care following circumcision includes assessment for symptoms of bleeding every 30 minutes for at least 2 hours. Assessment and documentation of the first void following circumcision are also necessary to evaluate for urinary obstruction related to penile injury or edema. Petroleum gauze should be applied to the circumcision site and should be changed frequently to protect the site and prevent bleeding. Parent education prior to discharge is necessary and should include care of the site as well as potential complications requiring medical care. Parents should be told that normal bathing is safe and be provided instructions regarding the petroleum-based dressing. Parents should also be advised to seek medical care if the child presents with pain, fever, lethargy, separation of the edges of the skin, unusual swelling or bleeding, and difficulty with urination.

ACUTE RENAL FAILURE

Pathophysiology

Acute renal failure (ARF) is associated with a significant increase in both the mortality and the morbidity of infants in the NICU. ARF occurs when the GFR abruptly decreases or completely ceases, leading to impairment in fluid and electrolyte regulation and acid–base homeostasis (Jetton & Askenazi, 2014). ARF can be either oligoanuric or nonoliguric. Oligoanuric renal failure is suspected when urinary output falls below 1 mL/kg/hour and serum creatinine levels rise to greater than 1.5 mg/dL. Nonoliguric renal failure occurs in 30% of cases and has an elevated creatinine level, but urine output is either normal or elevated. Other indicators of ARF include a serum creatinine level that rises by 0.3 mg/dL within the first 48 hours or rises 50% or higher above baseline (Jetton & Askenazi, 2014; Selewski et al., 2015).

ARF can be classified as prerenal, intrinsic, or postrenal. Prerenal failure is by far the most common, accounting for 75% to 80% of cases, and is caused by inadequate perfusion to a normal kidney (Nada, Bonachea, & Askenazi, 2017). Decreased perfusion may be caused by increased fluid losses from hemorrhage, increased insensible water loss, third spacing, or by decreased renal blood flow due to congestive heart failure, hypotension, or hypoxia (Nada et al., 2017). Persistent hypoxia may lead to shunting of blood away from the kidneys toward the more critical organs of the body, causing renal hypoperfusion. Failure to adequately recognize and treat prerenal failure can result in permanent kidney damage.

Intrinsic renal failure results from damage to the renal parenchyma and can occur due to progression of either prerenal or postrenal failure, infection, renal vein thrombosis (RVT), or nephrotoxicity from medications such as aminoglycosides, indomethacin, and amphotericin B (Girardi et al., 2017; Nada et al., 2017; Selewski et al., 2015). Acute tubular necrosis (ATN) is the most common cause of intrinsic renal failure and is a renal tubular cellular injury due to severe hypoxia, dehydration, sepsis, or blood loss (Nada et al., 2017). Other causes of intrinsic renal failure include structural abnormalities of the kidney, including renal

dysplasia and polycystic or multicystic kidney disease (MKD; Nada et al., 2017).

Postrenal failure is caused by obstruction of the urinary tract with resultant disruption in antegrade urine flow (Nada et al., 2017). Posterior urethral valves (PUVs), UPJ and ureterovesical junction obstruction, prune-belly syndrome, and neurogenic bladder can cause obstruction. Back flow of urine into the kidney pelvis can result in hydronephrosis and subsequent damage to the renal parenchyma.

Risk Factors

Acute kidney injury is common in neonates and is estimated to occur in 24% to 56% of neonates admitted to the NICU (Lee et al., 2017). This estimate may not accurately reflect the true incidence since cases of nonoliguric renal failure are often not included. Any condition that interferes with normal renal function can cause acute injury (Table 18.3). Asphyxia is one of the most common causes of ARF, with 30% to 56% of affected infants having ARF (Chock, Frymoyer, Yeh, & Van Meurs, 2018). Severity of the asphyxia correlates with both the incidence and the severity of ARF, and the risk increases during hypothermic therapy. ARF is also common in very-low-birth-weight infants, with the most premature infants being the most susceptible to injury (Lee et al., 2017).

Clinical Manifestations

Acute renal injury should be suspected in all critically ill infants in the NICU, especially those with underlying risk factors for ARF. Cardinal symptoms of ARF include urine output less than 1 mL/kg/hour and an elevated creatinine level. However, oliguria is not always present since infants with nonoliguric renal failure may have a normal or high urine output. The infant may also appear edematous due to fluid overload resulting from a decreased urinary output and be hypertensive from fluid overload or an increased secretion of renin and aldosterone from the damaged kidney. Physical examination may reveal a flank mass, abnormal genitalia, or the presence of other associated congenital anomalies.

Serum electrolytes will show an elevated BUN and creatinine level and, possibly, hyperphosphatemia, hyponatremia, acidosis, and hypocalcemia. Hematuria and proteinuria on urine dipstick and urinalysis are also common signs of intrinsic renal failure (Joseph & Gattineni, 2016). A urine to plasma osmolality ratio of 1:1 or less is also indicative of renal failure. Renal compromise can be detected in utero through evaluation of fetal urine samples. The maximum fetal urine electrolyte levels considered within normal limits are sodium, 100 mEq/L; chloride, 90 mEq/L; and osmolality, 210 mOsm/kg. When these levels are elevated, renal failure is suspected.

TABLE 18.3

MAJOR CAUSES OF ACUTE RENAL FAILURE IN THE NEWBORN

Prerenal Failure	Intrinsic Renal Failure	Postrenal Failure
Systemic hypovolemia	Acute tubular necrosis	Congenital malformations
Fetal/neonatal hemorrhage	Congenital malformations	Imperforate anus
Septic shock	Bilateral agenesis	Urethral stricture
Necrotizing enterocolitis	Renal dysplasia	
Polycystic kidney disease	Posterior urethral valves	
Dehydration		Urethral diverticulum
Renal hypoperfusion	Glomerular immaturity	Primary vesicoureteral reflux
Perinatal asphyxia	Infection Congenital syphilis	
Congestive heart failure	Toxoplasmosis	Ureterocele Megacystis megaureter
Cardiac surgery	Pyelonephritis	
Respiratory distress syndrome	Renal vascular Renal artery thrombosis	Eagle–Barrett syndrome (prune-belly syndrome)
Pharmacological	Renal venous thrombosis	

(*continued*)

TABLE 18.3

MAJOR CAUSES OF ACUTE RENAL FAILURE IN THE NEWBORN (*continued*)

Prerenal Failure	Intrinsic Renal Failure	Postrenal Failure
Tolazoline	Disseminated intravascular coagulation	Ureteropelvic junction obstruction
Captopril		
Indomethacin		Extrinsic compression
	Nephrotoxins	
	Aminoglycosides	Sacrococcygeal teratoma
	Indomethacin	
	Amphotericin B	Hematocolpos
	Contrast media	Intrinsic obstruction
	Intrarenal obstruction	
		Renal calculi
	Uric acid nephropathy	Fungus balls
		Neurogenic bladder
	Myoglobinuria	
	Hemoglobinuria	

Source: Modified from Vogt, B. A. & Dell, K. M. (2015). The kidney and urinary tract. In R. J. Martin, A. A. Fanaroff, & M. C. Walsh (Eds.), *Neonatal-perinatal medicine: Diseases of the fetus and infant* (10th ed., Vol. 1). St. Louis, MO: Elsevier Saunders.

Diagnosis

ARF is often a manifestation of other underlying disease processes, and diagnosis is aimed at both determining the presence of ARF and identifying the causative element. The suspected contributing process determines specific diagnostic testing.

A careful prenatal, perinatal, and postnatal history is necessary when evaluating an infant with symptoms of renal failure. A family history and prenatal history, including prenatal ultrasound results and amniotic fluid measurements, should be evaluated. Information should be collected regarding a history of perinatal depression, conditions associated with decreased renal blood flow, and administration of nephrotoxic medications.

To differentiate between prerenal and intrinsic renal failure, a fluid challenge of 10 to 20 mg/kg of an IV isotonic solution may be administered (Nada et al., 2017). A urine output of at least 1 mL/kg/hour within 2 hours of the fluid infusion strongly suggests a prerenal cause for the renal failure. The use of a diuretic following the fluid challenge may be necessary if urine output does not immediately increase. A fractional excretion of sodium (FeNa) and a renal failure index may be calculated to further differentiate between prerenal and intrinsic renal failure. A FeNa greater than 3% and a renal failure index greater than 3 suggest a prerenal etiology. Unfortunately, both of these indices are only accurate after 48 hours following delivery, suggesting a need for alternative mechanisms for acute kidney injury within the first 48 hours of life. Urinary biomarkers are under investigation and may be more specific markers for renal tubular damage.

Postrenal failure originating in the lower urinary system can be diagnosed by a positive urinary output following placement of a urinary catheter. A renal ultrasound is indicated to evaluate the etiology of both intrinsic and postrenal failure. Other diagnostic testing is indicated by individual clinical manifestations and suspected underlying etiology of the renal failure.

Prognosis

The prognosis of ARF is related to both the severity of the underlying disease and the ability to treat the underlying problem. The presence of ARF is an independent risk factor for infant mortality and is associated with both short- and long-term complications (Harer, Pope, Conaway, & Charlton, 2017; Maqsood, Fung, Chowdhary, Raina, & Mhanna, 2017). At least 40% of infants diagnosed with ARF experience residual renal dysfunction and/or HTN, and a long-term follow-up is necessary.

Collaborative Management

Early recognition and treatment of ARF may prevent further renal failure and improve outcome, and therefore, the overall treatment goal is to prevent long-term complications of ARF. ARF is treated symptomatically until a definitive cause is determined to guide more specific treatment. Increasing renal perfusion through administration of increased intravascular fluids and, possibly, administration of low-dose dopamine treats prerenal failure.

In infants with intrinsic renal failure, fluid administration is limited to replacement of insensible water losses, other fluid losses, and urine output. Accurate calculation of fluid intake, electrolytes, and urine output is vital to prevent fluid overload and subsequent HTN, edema, and hyponatremia. Hyponatremia can occur because of fluid overload due to oliguria and increased renal sodium losses in infants with nonoliguric renal failure (Misurac, 2017; Nada et al., 2017). Although treatment with fluid restriction is usually sufficient, if the infant is symptomatic or the serum sodium level is less than 120 mEq/L, correction with 3% hypertonic 5 mL/kg over 4 to 5 hours may be necessary (Nada et al., 2017). Hyponatremia unresponsive to treatment may require dialysis.

Since the kidney excretes excess phosphorus, hyperphosphatemia can occur in infants with renal failure. Treatment includes phosphorus restriction, use of low-phosphate formula, and administration of oral calcium carbonate, which binds phosphate and prevents absorption (Nada et al., 2017). Hypocalcemia is also common and may require additional calcium supplementation.

The kidney excretes potassium; therefore, infants with intrinsic renal failure are at significant risk of hyperkalemia. Due to the possibility of cardiac rhythm abnormalities, hyperkalemia can be life-threatening, and thus, potassium intake should be significantly limited or eliminated and the serum level carefully monitored (Nada et al., 2017). Fresh blood should be used for transfusions since older blood is more likely to contain hemolyzed cells, with a resultant elevation in potassium. Treatment of hyperkalemia includes administration of sodium bicarbonate and a combination of insulin and dextrose to drive potassium from the intracellular space into the extracellular space, thereby reducing the serum level of potassium. Administration of IV calcium can be used to protect the heart against arrhythmias but does not reduce the serum potassium level. Kayexalate can be administered rectally to increase elimination of potassium through the intestinal tract. Kayexalate may be ineffective in infants less than 29 weeks' gestation and may be contraindicated due to a possible increased risk of necrotizing enterocolitis (NEC). Uncontrolled hyperkalemia is the most common reason that dialysis is necessary.

Since the kidneys excrete excess hydrogen from the body, metabolic acidosis is common in infants with intrinsic renal failure. Treatment with either additional sodium acetate in IV fluids or administration of sodium bicarbonate orally or parenterally may be necessary (Coulthard, 2016). Sodium bicarbonate should be administered with caution due to its hypertonic nature and possibility of increasing the risk of intraventricular hemorrhage in premature infants.

Due to decreased production and release of erythropoietin from the affected kidney, anemia is a potential complication of renal failure. Careful monitoring of the hematocrit is essential, and treatment with exogenous erythropoietin or packed red blood cell transfusion may be necessary (Coulthard, 2016).

HTN secondary to fluid overload or increased renin secretion from the damaged kidney is common and may require treatment with sodium and fluid restriction. Antihypertensive agents, such as hydralazine, nicardipine, and nitroprusside, may be required if the HTN is severe and/or uncontrollable (Misurac, 2017).

Because many medications are eliminated through the kidney, certain drugs including aminoglycosides, penicillins, cephalosporins, theophylline, indomethacin, tolazoline, amphotericin, and magnesium should be used with caution and levels carefully monitored (Hanna, Askenazi, & Selewski, 2016).

Adequate nutrition is critically important to prevent catabolism and malnutrition but is challenging due to the necessary protein and fluid restriction. Because of their decreased sodium potassium and phosphorous loads, infants receiving enteral nutrition may benefit from feedings of breast milk, Similac PM 60/40, or SMA. Infants with intrinsic renal failure are unable to excrete the by-products of protein breakdown with subsequent elevation in BUN and ammonia levels. Protein administration is thereby generally limited to 1 to 2 g/kg/day.

Emergency Alert: If the infant's condition continues to deteriorate and high BUN and creatinine levels coupled with increasing ammonia levels are present, dialysis may be necessary. Dialysis is a process that removes solutes by diffusion from across a semipermeable membrane (Rees, 2017). Dialysis is generally indicated when maximal medical therapy has failed, and specific recommendations include hyperkalemia, severe hyponatremia, acidosis, hypocalcemia, hyperphosphatemia, volume overload, and malnutrition (Nada et al., 2017; Rees, 2017; Selewski et al., 2015). Although survival of infants requiring dialysis has increased over the past several decades, it remains challenging in neonates (Coulthard, 2016).

Currently, two types of dialysis are used in neonatal patients: peritoneal dialysis and hemofiltration. Peritoneal dialysis is simple, less invasive, is associated with improved hemodynamic tolerance, and is currently the most common type of dialysis performed in neonates (Misurac, 2017; Nada et al., 2017; Selewski et al., 2015). During peritoneal dialysis, hyperosmolar dialysate is infused into the peritoneal cavity through a surgically placed Silastic Tenckhoff catheter, and following dialysis, the fluid is drained from the cavity. Depending on the need for solute and fluid removal, cycle time, dwell time, volume, and the osmolar concentration of the fluid can be adjusted.

Hemofiltration is used when peritoneal dialysis is contraindicated, such as in infants with NEC or those who have undergone abdominal surgery (Selewski et al., 2015). Hemofiltration is a continuous filtration process and includes continuous arteriovenous and continuous venovenous hemofiltration. Continuous arteriovenous hemofiltration (CAVM) involves cannulation of both an artery and a vein. Blood is removed via the artery driven across a filter and replaced via the vein. Continuous venovenous hemofiltration involves either cannulation of two veins or placement of a double-lumen venous line, and a pump is used to draw blood into the filtration circuit.

Nursing Management

Accurate calculation of fluid intake and output is vital to prevent fluid overload and its associated HTN, hyponatremia, and edema (Nada et al., 2017). Frequent monitoring of electrolytes is essential to assess for abnormalities, including hyponatremia (Selewski et al., 2015), which, if severe, can result in seizures, and hyperkalemia, which may produce life-threatening cardiac arrhythmias. Careful monitoring for cardiac arrhythmias using bedside EKG monitoring in infants with intrinsic renal failure at risk for hyperkalemia is necessary. Vital signs, activity level, and color should be frequently assessed to ensure that subtle changes indicating anemia are promptly detected. Infants with renal failure are prone to infection due to multiple invasive procedures and their extended hospitalization and, therefore, should be monitored for signs of infection and any abnormality reported to ensure timely diagnosis and treatment.

Nursing responsibilities for infants on dialysis include monitoring the equipment, monitoring the cycles if performed manually, performing clotting studies, and administration of heparin and other drugs via the dialysis apparatus. Catheter care includes maintenance of aseptic technique, prevention of hemorrhage and clotting, and observation of the insertion site for signs of infection or dislodgment. The infant should be observed for signs and symptoms of chemical imbalances during the entire dialysis procedure. Accurate measurement of fluid intake and output and electrolyte levels is critical. Fluid shifts affecting blood pressure and electrolyte balance can occur rapidly, causing cardiac arrhythmias, muscle spasms, seizures, and shock.

SEVERE OLIGOHYDRAMNIOS SEQUENCE (FORMALLY POTTERS)

Pathophysiology

Severe oligohydramnios sequence occurs in approximately 1 in 10,000 births with an increased incidence in males. Defects associated with this syndrome can be due to bilateral renal agenesis resulting when the ureteric bud fails to divide and develop, culminating in complete absence of the kidney (Phua & Ho, 2016). The etiology can also include completely dysfunctional kidneys due to autosomal recessive polycystic kidney disease (ARPKD), dysplastic kidneys, renal hypoplasia, and obstructive uropathies. The developing fetus continuously swallows amniotic fluid, which is absorbed by the gastrointestinal system and is then secreted into the amniotic cavity by the kidney. When there is little to no urinary output, severe oligohydramnios occurs, resulting in the deformities seen in severe oligohydramnios sequence. An adequate amount of amniotic fluid is also necessary for normal pulmonary development. In the presence of severe oligohydramnios, normal pulmonary development fails to occur, resulting in development of hypoplastic lungs.

Diagnosis

Infants are often born premature, small for gestational age, and in the breech position. Many affected fetuses are stillborn. The effect of severe oligohydramnios on the facies includes low-set, malformed ears and micrognathia, "senile" appearance, wrinkled skin, parrot-beak nose, and wide-set eyes with epicanthal folds. Depending on the degree of oligohydramnios, variable degrees of respiratory distress due to pulmonary hypoplasia are present. Contractures of the limbs due to intrauterine compression are common.

Severe oligohydramnios sequence is readily identifiable on direct observation because of its characteristic features. Prenatal history includes severe oligohydramnios and bilateral renal agenesis or other renal disorders. Regardless of prenatal ultrasound results, an abdominal ultrasound following birth is indicated to confirm the diagnosis.

Collaborative Management

Severe oligohydramnios sequence is almost universally fatal due to pulmonary hypoplasia and subsequent respiratory failure. Due to the irreversible pulmonary hypoplasia, treatment does not include renal transplantation or long-term dialysis.

Assisting the family to cope during and after the death of their infant is the primary aspect of nursing care of infants with severe oligohydramnios sequence. The nurse should encourage parents to visit and hold their infant. Support from pastoral services or social work is imperative during this difficult time.

UNILATERAL RENAL APLASIA

Pathophysiology

When one of the ureteric buds fails to form in utero, unilateral renal aplasia, or the absence of one kidney, occurs. The incidence of unilateral renal aplasia may be as high as 1 in 500 births and is often associated with other structural defects, such as VACTERL association (vertebral anomalies, tracheoesophageal atresia, esophageal atresia, renal agenesis, renal dysplasia, and limb defects), caudal regression syndrome, and chromosomal abnormalities. This condition may often go undetected in the newborn period and may be an incidental finding later in life.

Clinical Manifestations

If the unaffected kidney is normal, infants with unilateral renal aplasia are often asymptomatic (Davidovits, Cleper, Eizenberg, Hocherman, & Mashiach, 2017). Unfortunately, the contralateral kidney is often abnormal, and findings of VUR, UPJ obstruction, renal dysplasia, and ureterocele are common. When the contralateral kidney is abnormal, symptoms are directly related to the type of renal abnormality. If function of the remaining kidney is significantly decreased, the infant may exhibit signs of renal failure. Diagnosis centers on confirmation of the presence of a single kidney and investigation of the contralateral kidney for abnormalities. This is best accomplished by renal ultrasonography with future testing being determined by results of the ultrasound.

Collaborative Management

If kidney function is not compromised, no nursing care beyond normal newborn care is usually necessary. Information regarding the nursing care and treatment of the specific disorders affecting the contralateral kidney is contained in the appropriate section. The prognosis for infants diagnosed with unilateral renal atresia is excellent if the contralateral kidney is normal. If the remaining kidney is abnormal, the prognosis depends on the specific disease process.

CYSTIC KIDNEY DISEASE

Cystic disease of the kidney occurs when normal kidney tissue is replaced with nonfunctioning cysts. These cysts may occur unilaterally or bilaterally, and the amount of cystic formation within each kidney determines the severity of the disease. Severely affected kidneys often have an associated ureteral agenesis. Cystic kidney disease includes polycystic kidney disease and MKD.

POLYCYSTIC KIDNEY DISEASE

Pathophysiology

Polycystic kidney disease is a bilateral process involving micro- or macroscopic cysts distributed throughout the renal parenchyma (Dell, 2011). There are two types of polycystic kidney disease: autosomal dominant polycystic kidney disease (ADPKD) and ARPKD. ADPKD rarely presents in the neonatal period, with symptoms presenting in the fourth to fifth decades of life. In contrast, ARPKD presents in the neonatal period with enlarged kidneys and replacement of the kidney parenchyma with nonfunctional cysts (Figure 18.5). The pelvis, calyces, and ureter are all normal (Baum, 2015). Liver involvement, including hepatic fibrosis, is nearly universal, but symptoms rarely occur in the neonatal period (Hoyer, 2015).

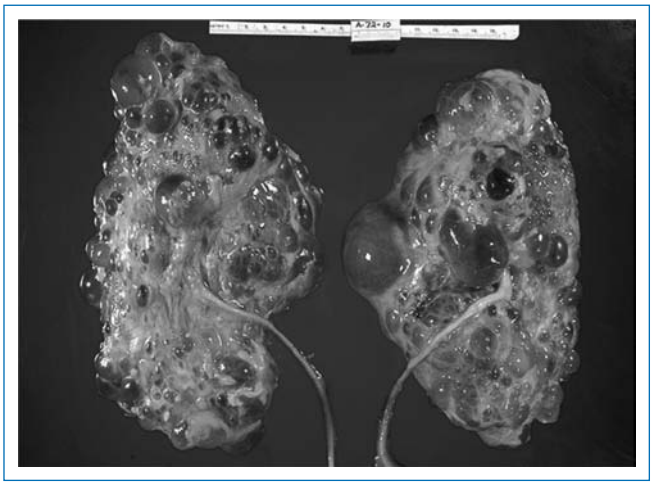

FIGURE 18.5 Gross specimen showing polycystic kidney disease.

Source: Jnah, A. J., & Trembath, A. N. (Eds.). (2019). *Fetal and neonatal physiology for the advanced practice nurse.* New York, NY: Springer Publishing Company.

Risk Factors

The incidence of ARPKD is 1 in 10,000 to 1 in 40,000 (Dell, 2011; Mao, Francis-West, & Irvine, 2015). The majority present as a sporadic anomaly, but an association with other syndromes has been reported. The genetic cause of ARPKD is mutations in the *PKHD1* gene located on chromosome 6p21 (Mao et al., 2015).

Clinical Manifestations

Symptoms include bilateral abdominal masses and HTN. Respiratory distress may also be present due to pressure from the enlarged kidneys on the diaphragm or from pulmonary hypoplasia due to oligohydramnios (Hoyer, 2015).

Diagnosis

ARPKD may be diagnosed on prenatal ultrasound showing enlarged kidneys with increased echodensity. Postnatal diagnosis is through ultrasound findings of small cysts in the collecting ducts. After discussion with the family, a positive family history for ARPKD is often discovered.

Prognosis

Six to thirty percent of affected infants will die in the neonatal period, usually as a result of respiratory failure from pulmonary hypoplasia (Dell, 2011; Mao et al., 2015; Phua & Ho, 2016). In those who survive the neonatal period, over 80% are alive at 10 years (Marlais et al., 2016). An additional close to 60% of infants will eventually advance to end-stage renal disease, requiring dialysis and renal transplantation. Hepatic complications are common and include portal HTN and biliary disease (Dell, 2011).

Collaborative Management

Treatment of ARPKD is mainly supportive and includes treatment of renal failure, ventilatory support if significant respiratory distress is present, and treatment for HTN. HTN associated with ARPKD may be difficult to control, requiring treatment with fluid restriction and antihypertensive medications (Marlais et al., 2016). Nephrectomy may be indicated if severe respiratory distress occurs due to pressure on the diaphragm and/or lungs from the enlarged kidney (Misurac, 2017).

MULTICYSTIC KIDNEY DISEASE

Pathophysiology

MKD is characterized by a collection of different-sized noncommunicating cysts with a complete lack of renal function due to early obstruction of the ureter leading to kidney maldevelopment (Baum, 2015). MKD is generally a unilateral disease; however, if both the kidneys are affected, the prognosis is grim due to respiratory failure from pulmonary hypoplasia.

Risk Factors

MKD has an incidence of 4.3 in 10,000 (Winding et al., 2014).

Clinical Manifestations and Diagnosis

The majority of cases are diagnosed via antenatal ultrasound (Winding et al., 2014). If not diagnosed prenatally, most infants present with a palpable flank mass. Postnatal diagnosis is through renal ultrasound, indicating multiple noncommunicating renal cysts with no normal renal parenchyma or renal pelvis (Sarhan et al., 2014). A radionuclide renal scan will indicate a complete lack of renal function of the affected kidney. VUR and UPJ obstruction frequently occur in the contralateral kidney, requiring careful evaluation via ultrasound and VCUG (Tiryaki et al., 2013). The contralateral kidney is at risk for decreased function both in the neonatal period and childhood.

Collaborate Management

Historically, management included nephrectomy of the affected kidney to confirm diagnosis and prevent HTN and renal malignancy. It is now known that spontaneous involution of the multicystic kidney generally occurs and that only a minimal risk of either HTN or malignancy exists (Chiappinelli, Savanelli, Farina, & Settimi, 2011). Spontaneous involution of the multicystic kidney occurs in 33% of cases, and therefore, conservative treatment is often recommended (Tiryaki et al., 2013). Follow-up care includes clinical and ultrasound assessment every 6 months for the first 2 years and yearly afterward until complete involution of the kidney occurs (Chiappinelli et al., 2011). Proponents of prophylactic nephrectomy argue that frequent follow-up is burdensome to both the family and child and that more cost is incurred than with early removal of the kidney (Tiryaki et al., 2013). Since long-term dysfunction in the remaining kidney is common, careful long-term evaluation for renal function is warranted.

PRUNE-BELLY SYNDROME (EAGLE–BARRETT SYNDROME)

Pathophysiology

Prune-belly syndrome consists of a triad of anomalies, including lack of appropriate abdominal musculature, undescended testicles, and urinary tract malformations (Figure 18.6; Garcia-Roig et al., 2016; Misurac, 2017). Associated urinary abnormalities include an enlarged, poorly functioning bladder; VUR; and urethral obstruction. The ureters may be tortuous and severely dilated, and the kidneys may be dysplastic due to urinary tract obstruction with reflux of urine into the kidneys. Other associated abnormalities include orthopedic, cardiovascular, and respiratory anomalies as well as imperforate anus and patent urachus (Hassett, Smith, & Holland, 2012; Seidel, Arlen, Smith, & Kirsch, 2015).

Two theories exist concerning the etiology of prune-belly syndrome. The first suggests that in utero urethral obstruction results

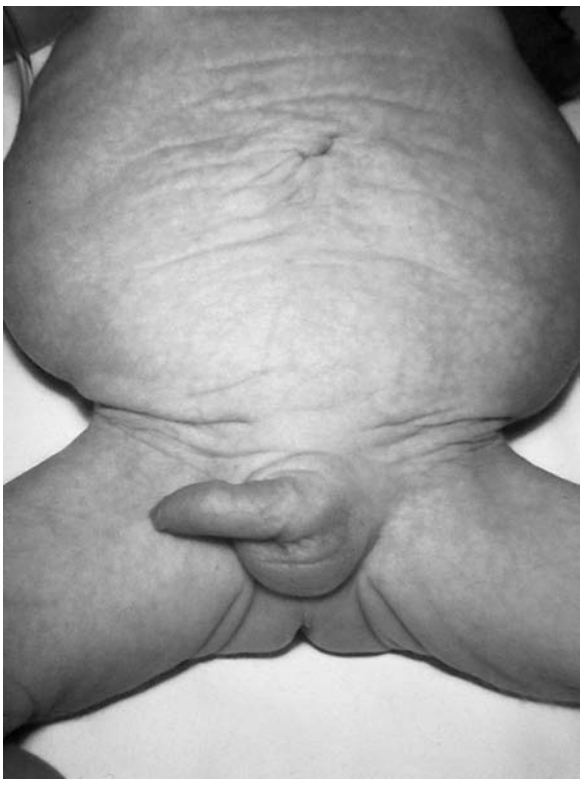

FIGURE 18.6 A neonate with prune-belly syndrome.
Source: From Clark, D. (2000). *Atlas of neonatology.* Philadelphia, PA: Saunders.

in a back flow of urine into the bladder, leading to severe bladder dilation. This extreme dilation places pressure on the abdominal muscles with subsequent abnormal abdominal wall muscle development (Herman & Siegel, 2009). The second and most prevalent theory is that a generalized mesodermal abnormality occurs during the fourth to 10th weeks of fetal development. During this time, the bladder is taking shape and is being separated from the allantois, and formation of the abdominal wall is occurring. The abnormal mesodermal development leads to the triad of defects seen with prune-belly syndrome (Misurac, 2017).

Risk Factors

Prune-belly syndrome predominantly affects males and only rarely occurs in females. It is 20 times more common in males and has an incidence of approximately 4 in 100,000 live births (Lloyd et al., 2013).

Clinical Manifestations

If the abdominal muscles are severely weakened, the abdominal region may appear wrinkled, much like a prune's surface. Due to the lack of abdominal musculature, there may be visible bowel loops and observable spleen and liver. The abdomen will feel flaccid, and there will be a lack of muscle tone. A large distended bladder and large kidneys will be present on palpitation. Although the spleen is rarely palpable in neonates, one can often feel the spleen in infants with prune-belly syndrome is due to lack of abdominal muscle tone. The liver may also be easily palpable, with more than 1 to 3 cm of liver appreciated even if no hepatomegaly is present. Bilateral cryptorchidism is nearly universally present in males (Seidel et al., 2015). Infants with pulmonary hypoplasia due to oligohydramnios may present with varying degrees of respiratory distress, and those with cardiac anomalies may have symptoms of congenital heart disease.

Diagnosis

A diagnosis of prune-belly syndrome can be made as early as 13 weeks' gestation on prenatal ultrasound (Papantoniou et al., 2010). Oligohydramnios may be present if fetal renal function is compromised. The presence of a distended bladder, dilated ureters, large kidneys, and an abnormal abdominal wall on prenatal ultrasound is highly suggestive of prune-belly syndrome. Following birth, the diagnosis of prune-belly syndrome is generally obvious upon initial examination. A postnatal ultrasound will indicate bladder and urethra distension, hydroureter, and hydronephrosis. Determination of renal function is necessary, and an electrolyte panel including creatinine and BUN levels should be obtained. Urinary output and fluid status must be meticulously monitored. Following stabilization, a VCUG is generally indicated to assess for VUR, and a radionuclide renal scan may be scheduled to determine the degree of renal function. MRI may be useful in further identifying anatomical and functional abnormalities (Garcia-Roig et al., 2016).

Woodard classified patients with prune-belly syndrome into three groups. The first group accounts for 20% of cases and presents with severe renal dysplasia and pulmonary hypoplasia and has a mortality rate of nearly 100%. The second group accounts for 40% of patients and presents with significant urinary tract abnormalities but adequate renal function. Future renal compromise may occur due to renal obstruction or infection. The third group, accounting for 40% of patients, presents with mild urinary tract abnormalities and normal kidney function (Woodard, 1978).

Prognosis

The prognosis of prune-belly syndrome is directly related to the severity of any underlying renal dysfunction, whether there is pulmonary hypoplasia, and the presence of other associated anomalies (Seidel et al., 2015). The mortality rate is 10% to 20%, and another 25% to 39% will develop chronic renal dysfunction, potentially requiring ultimate dialysis and transplantation (Seidel et al., 2015).

Collaborative Management

This triadic anomaly generally results in severe urinary tract complications. The bladder is usually extremely distended and has a large postvoid residual often requiring bladder decompression for prevention of stasis and resultant reflux of urine into the kidney. Bladder decompression generally requires bladder catheterization, and an urethrotomy may be required if urethral obstruction is present. If urinary stasis results in UTIs, a vesicostomy may be indicated (Seidel et al., 2015). Other urinary tract correction is dependent on the type and severity of the underlying abnormalities.

The main goal of therapy is preservation of existing kidney function. Urinary stasis, reflux, and infection can potentially lead to progressive deterioration in renal function. Careful monitoring and prompt diagnosis and treatment are necessary to preserve existing renal function. In infants with decreased renal function, careful attention to fluid and electrolyte balance, removal of wastes, and adequate nutrition for growth and development is required. Prophylactic antibiotics are usually recommended to decrease renal damage from UTIs.

The prenatal placement of a vesicoamniotic shunt may be considered in the presence of oligohydramnios, a large distended bladder, and severe hydronephrosis when there is evidence of functioning kidneys. This procedure has been successful in decreasing

the degree of oligohydramnios and its associated complications and improving subsequent renal function (Leeners, Sauer, Schefels, Cotarelo, & Funk, 2000).

Muscle tone has been shown to improve with time, but abdominoplasty may be performed to improve the appearance of the abdomen and has been shown to increase self-esteem and improve abdominal strength (Seidel et al., 2015). The resultant improvement in abdominal strength may also decrease constipation associated with an inability to perform the necessary Valsalva maneuver required for intestinal evacuation. Strengthening the abdominal muscles may also decrease the number of respiratory infections occurring due to lack of abdominal support and an inability to produce an effective cough as well as to improve the child's posture.

Undescended testes are present in males affected with prune-belly syndrome, and orchiopexy is generally recommended prior to 6 months of age to avoid potential future testicular cancer; however, it is often delayed for 1 year to allow repair in conjunction with urinary tract reconstruction (American Urological Association guidelines; Kolon et al., 2014). Some recommend a nonoperative approach unless significant renal compromise is present, whereas others feel early urinary reconstruction to eliminate urinary stasis, correct reflux, and improve bladder drainage is necessary. Early urinary reconstruction, bilateral orchiopexy, and abdominoplasty may be associated with improved results (Seidel et al., 2015).

Nursing Management

If bladder distention and urinary retention continue when the infant is ready for discharge, parents should be taught to empty the infant's bladder by intermittent catheterization. Parents must also be educated regarding the signs and symptoms of a UTI, such as increased irritability with urination, temperature instability, increase or decrease in urine output, and cloudy or foul-smelling urine. They must understand the importance of early detection and intervention to prevent long-term renal compromise. If a vesicostomy or other urinary diversion procedure has been performed, parents will need specific discharge instructions regarding care of the device.

Consideration of parental feelings concerning the physical appearance of their infant is mandatory. Because American culture places significant value on an individual's appearance, it may be difficult for parents to accept the loss of their "perfect" infant. Significant parental support from social and pastoral services may be necessary. To increase parent–infant interaction, nurses should attempt to include the family as much as possible in the daily care of their infant. Infants diagnosed with prune-belly syndrome often require frequent hospitalizations and several operative procedures, and it is necessary to prepare families for the long-term needs of their infant (Arlen et al., 2016).

EXSTROPHY OF THE BLADDER

Pathophysiology

Exstrophy of the bladder is a rare but severe congenital defect where the anterior abdominal wall fails to close at the point of the bladder (O'Kelly, Keefe, Herschorn, & Lorenzo, 2018). It is theorized that the defect occurs due to an overgrowth of the cloacal membrane, which disrupts closure of the abdominal wall. Timing of its rupture determines the severity of the defect. Exstrophy of the bladder is the most common condition in a spectrum of anomalies ranging from simple epispadias to classic bladder exstrophy (O'Kelly et al., 2018).

Risk Factors

The incidence of this defect is 1 in 30,000 to 1 in 50,000 live births, with males being affected more often than females (Siffel et al., 2011). It is most often an isolated malformation, and infants born weighing less than 1,500 g may be at higher risk (Reinfeldt Engberg, Mantel, Fossum, & Nordenskjold, 2016).

Clinical Manifestations

In classic bladder exstrophy, the bladder region appears open or uncovered, and the posterior wall of the bladder is exposed. Implantation of the ureters may be visible as urine continues to pass from the orifices. A concomitant defect exists in the genitalia, and males present with epispadias with a short, flat, and angulated penis. In the female, the labia do not meet in the midline, and there is a divided clitoris (Pierre, Borer, Phelps, & Chow, 2014). Exstrophy of the bladder is generally not associated with other anomalies, and the kidneys are generally normal. Prolapse of the rectum may also be evident prior to surgical correction. Failure of the pubic bones to meet anteriorly causes the hips to rotate outward (Pierre et al., 2014). Cloacal exstrophy is the most severe expression in this spectrum of anomalies and presents with all the features of classic bladder exstrophy along with an omphalocele, imperforate anus, spinal defects, and UPJ obstruction (Pierre et al., 2014). Neural tube defects and spinal dysraphisms are also commonly present.

Diagnosis

Prenatal ultrasound may suggest the presence of bladder exstrophy. However, a definitive prenatal diagnosis can only be made in approximately 25% of cases. Diagnosis often does not occur until after birth when the defect is obvious on visual inspection (Goyal, Fishwick, Hurrell, Cervellione, & Dickson, 2012; Figure 18.7).

Prognosis

Prognosis is generally favorable with most children leading nearly normal lives. Long-term complications include incontinence as well as sexual and fertility problems.

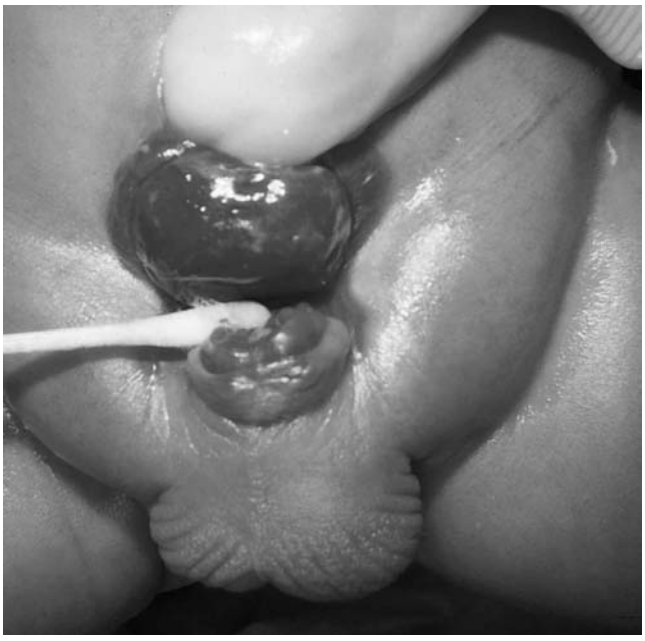

FIGURE 18.7 An infant with exstrophy of the bladder.
Source: From Clark, D. (2000). *Atlas of neonatology*. Philadelphia, PA: Saunders.

Collaborative Management

Treatment goals for infants with exstrophy of the bladder include successful bladder and abdominal wall closure, urinary continence, preservation of the upper urinary tract, and normal-appearing genitalia. Prior to or immediately following delivery, the infant should be transported to a tertiary care facility experienced with care of the infant with this defect (Inouye et al., 2018). Because bladder exstrophy exposes the urinary tract to the environment, careful attention to prevention of infection is essential both before and after surgical correction. Broad-spectrum antibiotic therapy is initiated prior to surgery and continued for at least 7 days. Because wound dehiscence is often caused by infection, strict observation of aseptic technique and aggressive management of infection are mandatory.

Repair may be accomplished in a single stage where the bladder is closed, the bladder neck is reconstructed, and the epispadias is repaired, usually around 6 weeks of life (O'Kelly et al., 2018). Repair may also be staged where there is a delay of epispadias repair and bladder neck reconstruction (O'Kelly et al., 2018). A suprapubic catheter and bilateral ureteral stents may be placed during surgery to allow drainage of urine while the bladder heals. The infant may be immobilized for several weeks following surgery with traction to facilitate wound healing. VUR is common but can generally be managed conservatively (O'Kelly et al., 2018). Due to the increased risk of future pregnancies being affected, genetic counseling is indicated (Suzuki et al., 2017).

Nursing Management

Immediately following birth, the exposed bladder should be covered with plastic wrap or a similar material to protect it from injury until closure is complete. The area should also be protected by avoiding gauze due to the possibility of becoming dry and adhering to the tissue, using a tie instead of a clamp for umbilical care, changing dressings as needed to prevent skin irritation, and using humidified incubators to prevent excess drying. Diapers should be kept folded well below the defect, to not only protect the area from irritation but to prevent wound infection.

RENAL VEIN THROMBOSIS

Pathophysiology

RVT is a rare occurrence in the neonate, potentially resulting in renal failure, renal atrophy, and HTN (Kraft, Brandao, & Navarro, 2011). The thrombus may be unilateral or bilateral and often extends into the inferior vena cava (IVC).

Risk Factors

RVT occurs in approximately 0.5 of 1,000 admissions to the NICU. Although the presence of an umbilical catheter is a risk factor, the majority of RVTs are non–catheter related, and the exact etiology is often unknown (Kraft et al., 2011). Up to 80% of affected infants have one or more risk factors, including male gender, hyperviscosity and polycythemia, perinatal asphyxia, maternal diabetes, prematurity, dehydration, and infection (Bidadi, Nageswara Rao, Kaur, Khan, & Rodriguez, 2016; Joseph & Gattineni, 2016). Most risk factors are thought to be related to an associated decreased kidney perfusion leading to vasoconstriction and a subsequent decreased venous blood flow and thrombosis. Neonates are at a higher risk for RVT than older children due to a low renal perfusion pressure, decreased levels of natural anticoagulants, and lower levels of fibrinolytic components (Resontoc & Yap, 2016).

Up to 50% of affected infants have inherited prothrombotic risk factors, including hypercoagulation disorders such as protein C deficiency, homocystinuria, and Factor V Leiden (Resontoc & Yap, 2016).

Clinical Manifestations

The mean age of onset is 3 days, with 7.3% of RVTs presenting in utero, 67% within the first 3 days following delivery, and 26% later than 3 days of life (Kraft et al., 2011). RVT often occurs in critically ill infants and may be incidentally discovered when the infant is imaged for other reasons. The classic triad of symptoms include a palpable flank mass, hematuria, and thrombocytopenia; however, only 13% to 22% of infants actually present with all three symptoms (Winyard et al., 2006). However, the majority of infants present with at least one of the three symptoms (Resontoc & Yap, 2016). Other clinical manifestations include symptoms of decreased renal function, including decreased urinary output, elevated creatinine, and anemia (Brandao, Simpson, & Lau, 2011; Resontoc & Yap, 2016).

Diagnosis

Diagnosis is through Doppler ultrasound showing an enlarged kidney. It also provides information regarding renal blood flow and may reveal the presence of a thrombosis located in the renal vein (Joseph & Gattineni, 2016; Resontoc & Yap, 2016). A radionuclide renal scan may be performed to assess function of the affected kidney. Since RVTs may not present with the typical triad of symptoms (flank mass, hematuria, and thrombocytopenia), a high degree of suspicion is necessary to increase the likelihood of prompt diagnosis and appropriate treatment.

Prognosis

Prognosis is dependent on the extent of the thrombus and on whether the lesion is unilateral or bilateral. Although the mortality rate is relatively low (5%) and often related to the underlying critical nature of the infant rather than the RVT, the risk of both acute and chronic complications is significant (Brandao et al., 2011). Acute complications include adrenal hemorrhage, thromboemboli, and pulmonary embolism. HTN, renal atrophy, and chronic renal failure, including end-stage renal disease, are long-term complications (Bidadi et al., 2016; Kraft et al., 2011). HTN occurs in 19% to 22% of survivors and may require nephrectomy if severe (Lau et al., 2007). Chronic renal insufficiency occurs in up to 71% of affected infants, with 3% of infants ultimately experiencing end-stage renal failure (Lau et al., 2007).

Collaborative Management

Treatment is dependent on the severity of the RVT, whether it is unilateral or bilateral, and the presence of impaired renal function (Resontoc & Yap, 2016). Currently, no specific guidelines exist for RVT treatment, and therapy varies between institutions and individual clinicians. Therapy may include supportive care; degradation of the clot with urokinase, streptokinase, or tissue plasminogen activator; or anticoagulation with low-molecular-weight heparin (Resontoc & Yap, 2016). If signs of renal failure occur, careful monitoring of fluid and electrolyte status is necessary as well as treatment of any HTN. In cases of severe renal failure, dialysis may be required. Due to the association of RVT with anticoagulant deficiencies, the infant will require a diagnostic workup for these disorders (Joseph & Gattineni, 2016). All infants will require long-term monitoring for HTN, renal atrophy, and chronic renal insufficiency.

Nursing Management

Nurses are essential for successful evaluation and treatment of RVT. They are often the first clinician to recognize the presence

of risk factors and clinical manifestations, and it is, therefore, necessary for nurses to have a strong knowledge base concerning RVTs. Careful monitoring for HTN is necessary as well as following dipstick urine analysis for hematuria and proteinuria. Strict monitoring of input and output as well as electrolyte status is also necessary. The use of thrombolytic agents or heparin requires careful monitoring of coagulation status, and extreme caution is warranted when using these agents in very-low-birth-weight infants due to the risk of intraventricular hemorrhage.

HYDRONEPHROSIS

Pathophysiology

Hydronephrosis is the accumulation of urine within the renal pelvis and calices to the point of overdistention. If left untreated, this buildup of fluid can cause irreversible kidney damage. Hydronephrosis can be caused by obstruction of urine flow at the UPJ, the ureterovesical valve, or the urethrovesical valve. Nonobstructive abnormalities such as VUR and prune-belly syndrome can also cause hydronephrosis. Secondary etiologies include obstruction such as kidney stones or tumors (Yang, Hou, Niu, & Wang, 2010). The severity of hydronephrosis is classified from grade I to grade V depending on the diameter of the renal pelvis.

Clinical Manifestations

Hydronephrosis is usually detected during a prenatal ultrasound. If the hydronephrosis is severe and bilateral, oligohydramnios may also be present. If diagnosis is delayed until after birth, hydronephrosis may present as a large, smooth, solid, palpable abdominal mass in the region of the kidney. Since the presence of an abdominal mass can signify many disease processes, including cystic kidney disease, urogenital tumors, and RVT, determination of the mass's etiology is essential.

Depending on the amount of functioning kidney, infants with hydronephrosis may have a decreased or normal urine output. When only one kidney is involved, urine output may be normal because a single kidney is sufficient for adequate removal of water and waste. Severe bilateral hydronephrosis may present with signs and symptoms of kidney failure, including a low or nonexistent urine output as well as a high creatinine and BUN level. Infants born with bilateral severe hydronephrosis may also exhibit features consistent with severe oligohydramnios sequence syndrome, including pulmonary hypoplasia due to the presence of oligohydramnios. Since UTIs may be associated with hydronephrosis, infants may present with signs of an UTI, including fever, subtle signs of sepsis, hematuria, proteinuria, and the presence of white blood cells on urinalysis (Joseph & Gattineni, 2016).

Diagnosis

Hydronephrosis is most commonly diagnosed on prenatal ultrasound and can be detected as early as 12 weeks' gestation by the presence of a dilated renal pelvis (Nguyen et al., 2010). Hydronephrosis is the most common renal abnormality detected prenatally and is present in 2.3% of all pregnancies (Ek, Lidefeldt, & Varricio, 2007).

The first diagnostic study indicated in infants suspected of having hydronephrosis or who have hydronephrosis on prenatal ultrasound is a renal ultrasound. In clinically stable infants, the ultrasound should be delayed until the infant is 3 to 4 days old, since the newly born infant's relative dehydration may mask the presence of hydronephrosis (Choi et al., 2016). If bilateral hydronephrosis, unilateral severe hydronephrosis, or possible PUVs exist, an ultrasound should be performed within 1 to 2 days (Nguyen et al., 2010). A VCUG is recommended to assess for the presence of reflux if the hydronephrosis is moderate or severe (Nguyen et al., 2010). Although administration of prophylactic antibiotics for prevention of UTI is somewhat controversial, many clinicians will prescribe until the presence of reflux has been excluded.

Prognosis

Prognosis depends on the underlying causative factor, the severity, and the presence of any permanent renal damage. Outcome ranges from complete resolution to end-stage renal disease requiring dialysis and renal transplant. Most cases of hydronephrosis occur without significant obstruction and can be managed conservatively without surgery (Di Renzo et al., 2015). Complications of hydronephrosis include HTN, UTI, and progressive renal damage (Oliveira, Oliveira, & Mak, 2016). Hydronephrosis secondary to VUR generally spontaneously resolves. Antenatally diagnosed hydronephrosis can indicate obstruction or other serious abnormalities, but can also represent a transient developmental change that may spontaneously resolve prior to birth. Even if resolved, postnatal imaging is required for at least 6 weeks (Choi et al., 2016).

Collaborative Management

Preservation of renal function is the main goal of treatment, and treatment is dependent on the severity of the hydronephrosis. Mild-to-moderate hydronephrosis is usually managed conservatively with close ultrasound monitoring. A VCUG is generally indicated to evaluate for VUR (Choi et al., 2016). Although severe hydronephrosis is initially managed with conservative treatment, some cases will ultimately require pyeloplasty due to deteriorating renal function. When reflux is present, prophylactic antibiotics are often prescribed for UTI prophylaxis.

When severe hydronephrosis is prenatally diagnosed, vesicoamniotic shunting (placement of a catheter into the bladder to drain urine) may be performed to reduce oligohydramnios and its associated complications as well as to sustain kidney function. After birth, definitive surgery is necessary to correct the obstructive defect or to provide a diversion for urine flow (Tubre & Gatti, 2015).

Nursing Management

Careful assessment is imperative in infants diagnosed with hydronephrosis. Vital signs, including blood pressure, must be monitored at least every 4 hours and more frequently if unstable. Monitoring blood pressure is especially important since HTN is a common complication in infants with severe hydronephrosis. Fluid and electrolyte status, including serum creatinine and BUN, must also be carefully monitored. Fluid intake and output should be recorded at least every 2 to 4 hours.

OBSTRUCTIVE UROPATHY

Pathophysiology

When obstruction occurs in the urinary tract, changes referred to as obstructive uropathy can occur. Obstruction to urinary flow can cause reflux of urine into the kidney, with resultant hydronephrosis and irreversible kidney damage (Misurac, 2017). Urinary obstruction can be unilateral or bilateral and can occur at the ureterovesical junction, the UPJ, or due to PUVs (Figure 18.8). The most common cause of urinary obstruction is UPJ obstruction. UPJ obstruction occurs due to obstruction of urinary flow from the pelvis of the kidney into the ureter and is caused by stenosis of the

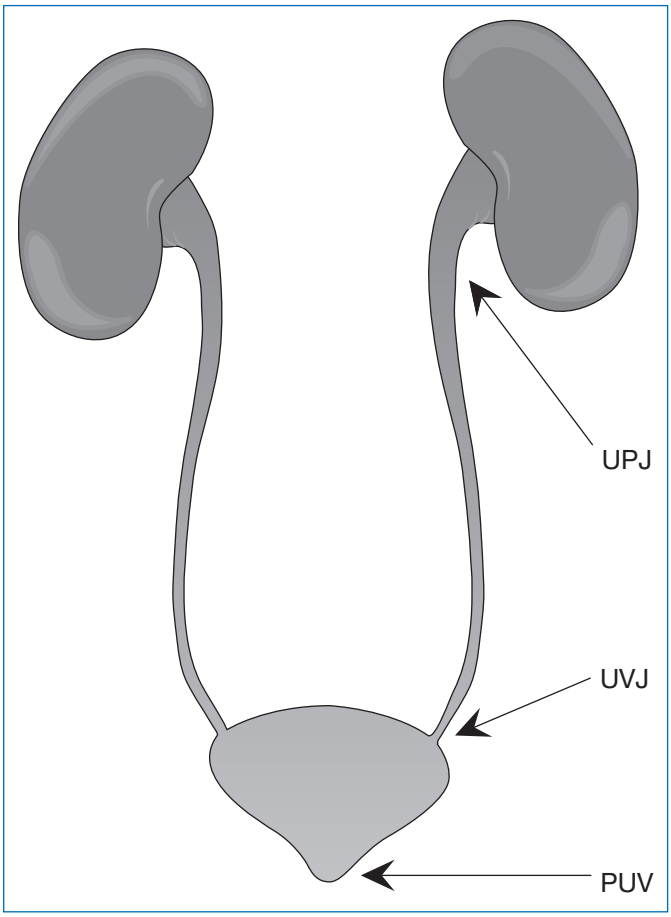

FIGURE 18.8 Location of most common sites of congenital urinary tract obstruction.

PUVs, posterior urethral valves; UPJ, ureteropelvic junction; UVJ, ureterovesical junction.

Source: From Chevalier, R. L. (2004). Perinatal obstructive nephropathy. *Seminars in Perinatology, 28*, 124–131. doi:10.1053/j.semperi.2003.11.009

ureter and/or its associated valves or by an insertion anomaly of the ureter (Choi et al., 2016). Ureterovesical junction obstruction is caused by obstruction of flow from the ureter into the bladder.

Risk Factors

UPJ obstruction is the most common cause of obstructive uropathy, with an incidence of 1 in 2,000, and is increased in males (Epelman et al., 2012). Information concerning PUVs may be found in the later section of this chapter.

Clinical Manifestations

Signs of urinary tract obstruction include symptoms of a UTI, or, if significant hydronephrosis is present, an abdominal mass may be appreciated. Severe, bilateral obstruction can also be associated with symptoms of renal failure.

Diagnosis

Urinary tract obstruction can be diagnosed on prenatal ultrasound as early as 16 to 17 weeks' gestation with evidence of hydronephrosis (Oliveira et al., 2016). Ultrasound findings range from mild hydronephrosis to extreme obstruction with oligohydramnios.

Postnatal diagnosis is via renal ultrasound and, although controversial, may be followed by a VCUG to assess for reflux (Weitz & Schmidt, 2017). A radionuclide renal scan is also recommended to assess renal function.

Prognosis

Obstructive uropathy can result in chronic renal failure and is a common cause of pediatric kidney transplantations if bilateral (Misurac, 2017).

Collaborative Management

Treatment depends on the severity of the obstruction and on whether the obstruction is unilateral or bilateral. If mild, conservative management is appropriate with frequent renal assessment. Prophylactic antibiotics may be indicated to prevent UTIs and the possibility of associated renal damage.

Surgical intervention may be indicated to relieve the obstruction. Insertion of a urinary diversion, such as a pyelostomy tube inserted into the renal pelvis, may be indicated (Hwang et al., 2018). Significant diuresis may follow urinary diversion, and thus, meticulous monitoring of fluid and electrolytes and replacement of losses are critical to avoid dehydration. Long-term follow-up is essential for the early detection of chronic renal problems (Tubre & Gatti, 2015).

Prenatal treatment, including insertion of a vesicoamniotic shunt, may be indicated if severe obstruction is present to increase the amniotic fluid volume and decrease the potential for renal failure. Complications of this procedure include shunt displacement and clogging of the shunt.

POSTERIOR URETHRAL VALVES

Pathophysiology

PUVs are the most common cause of urinary tract obstruction and cause severe obstruction uropathy, often resulting in end-stage renal failure (Odeh, Noone, Bowlin, Braga, & Lorenzo, 2016). PUV occurs when urine is obstructed at the level of the bladder outlet due to the presence of enlarged valves. Severity ranges from mild obstruction to severe disease, with obstructive uropathy and massive hydronephrosis. Urinary obstruction can increase pressure in the bladder and upper urinary tract, resulting in abnormal bladder function and renal injury (Casella, Tomaszewski, & Ost, 2012).

Risk Factors

PUV is a rare disease occurring exclusively in males with an incidence of 1 in 3,000 to 1 in 8,000 live births (Yohannes & Hanna, 2002). The specific etiology is unknown. Other associated urinary tract anomalies including VUR are common (Kibar, Ashley, Roth, Frimberger, & Kropp, 2011).

Clinical Manifestations

Neonatal symptoms of PUV include a palpable bladder, anuria or oliguria, a weak urinary stream, urosepsis, and urinary ascites (Kibar et al., 2011). If severe oligohydramnios is present prenatally, respiratory symptoms due to pulmonary hypoplasia may be present.

Diagnosis

PUVs are often diagnosed on prenatal ultrasound with the presence of bilateral hydronephrosis, a distended bladder, a dilated posterior urethra, and a thickened bladder wall (Casella et al., 2012). Following delivery, an ultrasound is required to evaluate the presence and degree of hydronephrosis, the presence of bladder wall thickening, and the general health of the kidneys. However, the gold standard for diagnosis is through a VCUG, showing a dilated posterior urethra, a trabeculated bladder, VUR, and sometimes

visualization of the enlarged valve leaflets. Renal scintigraphy for evaluation of renal function is usually deferred for approximately 4 weeks following birth to allow maturation of developing kidneys (Nasir, Ameh, Abdur-Rahman, Adeniran, & Abraham, 2011).

Prognosis

The diagnosis of PUVs is associated with significant long-term morbidity, which is dependent on the amount of renal damage caused by the PUVs (Caione & Nappo, 2011). In all, 13% to 42% of infants diagnosed with PUV will progress to end-stage renal disease, often requiring dialysis and/or renal transplantation (Caione & Nappo, 2011; Odeh et al., 2016). Bladder dysfunction in childhood is common, including bladder overactivity, resulting in urgency, urge incontinence, and nocturnal enuresis. The bladder can also become overdistended and overcompliant, causing ineffective bladder emptying and possibly requiring intermittent catheterization. Urethral strictures are also a possible complication occurring later in childhood (Caione & Nappo, 2011).

Collaborative Management

The initial treatment of PUVs is immediate urinary diversion with either bladder catheterization or suprapubic diversion to relieve the obstruction and reduce the pressure on the urinary tract to maintain normal bladder and kidney function (Misurac, 2017). Due to the increased risk of long-term complications, suprapubic diversion is only performed if bladder catheterization is impossible or if early correction of the defect is impossible because of the infant's small size or if the urethra is too small, precluding insertion of the endoscope for valve ablation. The infant may also require stabilization, including administration of IV fluids, correction of electrolyte or acid–base abnormalities, and antibiotics to prevent infection. Mechanical ventilation may be required if pulmonary hypoplasia is present. Definitive treatment of PUVs is transurethral endoscopic ablation (rupture) of the enlarged valves (Caione & Nappo, 2011). Prophylactic antibiotics are often required to prevent UTIs and subsequent renal injury, and long-term follow-up is essential to monitor bladder and renal function.

Unfortunately, prenatal treatment is difficult to perform and has not been shown to improve the mortality or morbidity of infants with PUV (R. K. Morris, Malin, Khan, & Kilby, 2010). In cases of oligohydramnios-associated pulmonary hypoplasia, some clinicians favor prenatal treatment with urinary diversion to increase the amniotic fluid level (R. K. Morris et al., 2010). In the future, prenatal valve ablation may be possible, thereby avoiding the renal and urinary tract damage that often occurs early in gestation prior to diagnosis of the defect (Casella et al., 2012).

Nursing Management

Immediately following delivery, the bladder should be catheterized under sterile conditions using a small 5- or 6-French feeding tube to allow passage through the constricted urethra. **Quality and Safety: Use of balloon catheters are contraindicated due to the possibility of bladder spasms.** Parents should be educated regarding the necessity of close postdischarge follow-up to ensure early detection of chronic renal disease and bladder dysfunction.

HYDROCELE

Pathophysiology

A hydrocele, the collection of fluid in the scrotal sac, is a common occurrence in the neonate (Lao, Fitzgibbons, & Cusick, 2012). The fluid originates from the peritoneal cavity, which communicates with the scrotum through a patent processus vaginalis. The only difference between the presence of a hydrocele and an inguinal hernia is the size of the processus vaginalis (Basta, Courtier, Phelps, Copp, & MacKenzie, 2015). If the processus vaginalis is small, only fluid can move into the scrotum, resulting in a hydrocele. Larger passageways may allow escape of a bowel segment into the scrotum, resulting in an inguinal hernia.

Risk Factors

The risk of a patent processus vaginalis is elevated with increased abdominal pressure secondary to a ventriculoperitoneal shunt or high ventilatory pressures and prematurity.

Clinical Manifestations

Clinical manifestations include the presence of painless scrotal swelling that is readily transilluminated.

Diagnosis

The most critical aspect of diagnosis is differentiating whether scrotal swelling is due to the presence of a hydrocele or the more serious diagnosis of either an inguinal hernia or testicular torsion. Upon palpation, inguinal hernias are generally reducible whereas hydroceles are not. When transilluminated, the hydrocele will show a fluid-filled scrotum, whereas an inguinal hernia will appear as a solid mass. If the examiner encounters loops of intestine near the vas deferens or the ductus deferens within the scrotal sac, an inguinal hernia is present. Ultrasound may also assist in differentiation (Basta et al., 2015).

Collaborative Management

Treatment for hydroceles is rarely indicated; the majority will spontaneously resolve within 1 to 2 years due to closure of the processus vaginalis (Basta et al., 2015). Indications for surgical correction generally include failure to resolve within the first year of life, although some surgeons will wait 2 years if there are no complications. Surgery entails drainage of fluid from the scrotal sac and closure of the processus vaginalis (Lao et al., 2012). Until resolution of the hydrocele, the infant should be closely monitored for signs of intestinal herniation. If an inguinal hernia is suspected, surgical intervention is indicated.

Nursing Management

Parents should be taught the signs of intestinal herniation and incarceration and the need for prompt medical attention if symptoms occur. These signs include the presence of a lump in the groin (this lump is especially noticeable when the infant is crying) and increased irritability. Careful attention must be paid to skin care of the edematous scrotum to avoid irritation and breakdown.

INGUINAL HERNIA

Pathophysiology

An inguinal hernia occurs when the intestines descend into either the inguinal canal or the scrotum through an open processus vaginalis (Lao et al., 2012; Figure 18.9). During fetal life, as the testes descend into the scrotum, they bring a small part of the peritoneum that is the processus vaginalis (Lao et al., 2012). When the processus vaginalis is open, fluid or intestines can pass through the opening, resulting in either a hydrocele or an inguinal hernia. The presence of a hydrocele or inguinal hernia is dependent on the size of the opening. The processus vaginalis becomes obliterated between 38 and 48 weeks of gestational age.

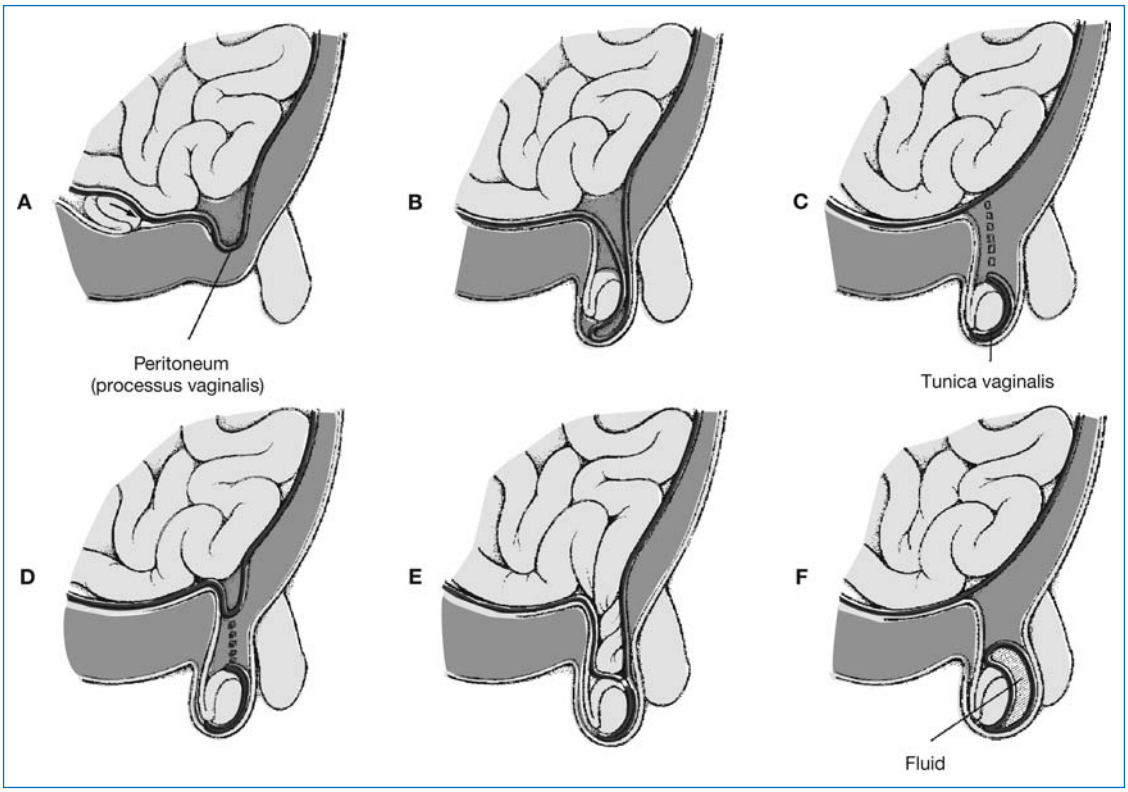

FIGURE 18.9 Development of inguinal hernias. (A and B) Prenatal migration of processus vaginalis. (C) Normal. (D) Partially obliterated processus vaginalis. (E) Hernia. (F) Hydrocele.

Source: From Hockenberry, M. J., Wilson, D., Winkelstein, M. L., & Wong, D. L. (2003). *Wong's nursing care of infants and children* (7th ed., p. 478). St. Louis, MO: Mosby.

Risk Factors

Due to the presence of an open processus vaginalis during fetal life, the incidence of inguinal hernias is inversely related to gestational age and birth weight. The incidence is also more prevalent in male infants (Youn et al., 2018). Sixty percent of inguinal hernias occur in the right and 15% are bilateral (Lao et al., 2012). Additional risk factors include cystic fibrosis, congenital hip dysplasia, the presence of a ventriculoperitoneal shunt, and abdominal wall defects.

Prognosis

The most severe complication of inguinal hernia is an incarcerated hernia with subsequent intestinal necrosis. The highest risk of incarceration occurs in early infancy, and the risk of incarceration in premature infants is up to 31% (Youn et al., 2018). When inguinal hernias are surgically repaired prior to incarceration, complications are rare. Reoccurrence after surgical repair can occur especially in infants born premature (Youn et al., 2018).

Clinical Manifestations

The most common clinical manifestation of an inguinal hernia is the presence of an inguinal bulge or mass as the omentum of the small intestine slides through the open processus vaginalis (Cavaliere, 2019). Crying or increased abdominal pressure often causes the inguinal hernia to appear more prominent. When a hernia is reducible, the intestine can be gently manipulated back into the abdomen cavity.

Diagnosis

The most important component of diagnosis is determining whether the mass is an inguinal hernia or other scrotal mass, including a hydrocele or testicular torsion. If the scrotum can be transilluminated, the mass may be either a hydrocele or an inguinal hernia (Cavaliere, 2019). Testicular torsion should be suspected if the scrotum contains a hard, solid mass. This is a surgical emergency and must be immediately reported to the surgical team. If it is not possible to distinguish between an inguinal hernia and a hydrocele, a rectal examination, while palpating the scrotum simultaneously, may reveal whether an intestinal loop is present in the scrotal sac rather than a fluid-filled hydrocele. The use of ultrasound may also prove helpful in differentiating between the two processes.

Collaborative Management

Inguinal hernias should be reduced daily and as needed by applying gentle pressure to assess for incarceration of the hernia. An incarcerated hernia occurs when the intestines are caught within the processus vaginalis. Symptoms of incarcerated hernias include inability to reduce, vomiting, a firm tense mass, inconsolable crying, and abdominal distention. When incarceration occurs, circulation is compromised and intestinal necrosis is possible, necessitating an immediate surgical consult.

If the inguinal hernia is nonreducible, advanced attempts for reduction are often attempted. After the infant is well sedated and placed in the Trendelenburg position, ice packs are placed on the hernia to reduce intestinal edema. If gentle reduction is successful, surgery may be delayed for 24 to 48 hours. Surgery for incarcerated hernias includes reduction of hernia and, if necrotic bowel is present, resection of the affected intestine.

Because of the high risk of incarceration, it is generally recommended that surgical repair of inguinal hernias should be performed as soon as possible. Surgery may be delayed in premature

infants due to the technical difficulty of operating and an increased risk of complications, including testicular atrophy and recurrent hernia. Exact timing of surgical intervention in the premature infant is controversial; however, many surgeons will correct the defect prior to discharge from the hospital (Gulack et al., 2018). Surgery may be performed either through an open procedure or through laparoscopic surgery (Ho, Ihn, Koo, Chang, & Oh, 2018). Surgical correction involves separation of the hernia sac from surrounding structures (Youn et al., 2018). The contralateral side may be explored to detect a patent process or a nonclinically evident hernia (Youn et al., 2018). Whether or not to explore the contralateral side is controversial. The goal of this exploration is to avoid future inguinal hernias, thereby reducing the risk of a second surgery and possible incarceration. However, it also increases the risk of infection, pain, and the cost of surgery. The risk of complications associated with surgical correction of inguinal hernias is generally low; however, premature infants are at high risk for postoperative apnea and should be monitored for at least 24 hours following surgery. Apnea following surgery may be decreased with the use of spinal anesthesia.

Nursing Management

Reduction of all inguinal hernias should take place daily, and an inability to reduce the hernia should immediately be reported to the medical and surgical team. The postoperative course is similar following open procedures or laparotomy and includes observation for apnea and adherence to aseptic technique with regard to suture line maintenance. The infant should be placed in a side-lying or supine position with the head turned to the side to prevent disruption of the suture line. Operative dressings should be observed for any drainage and bleeding, kept dry, and underlying skin should be regularly inspected for irritation and breakdown. Pain should be assessed every 4 hours, and appropriate pain management should be provided when indicated. Since discharge is often 24 hours after surgery, parents need to be instructed on proper surgical site and dressing care.

TESTICULAR TORSION

Pathophysiology

Torsion of the testicle occurs when the testis and coverings twist inside the scrotum, compromising blood flow, frequently resulting in a nonviable testicle (Basta et al., 2015).

Risk Factors

The incidence of testicular torsion is 6.1 per 100,000 (John, Kooner, Mathew, Ahmed, & Kenny, 2008). Although it is most often unilateral, bilateral torsion can unfortunately occur, resulting in complete lack of testicular development (Nandi & Murphy, 2011). Risk factors include vaginal delivery, prolonged labor, gestational diabetes, macrosomia, and breech delivery, and it appears that fetal stress and mechanical factors may be the contributing factors.

Prognosis

An 8.96% salvage rate for testicular torsion in the neonatal population has been reported. This may increase to 21.7% if surgery is emergent. Unfortunately, salvage of antenatally occurring torsion is extremely rare (Nandi & Murphy, 2011).

Clinical Manifestations

Testicular torsion presents with unilateral acute pain and scrotal swelling. The scrotum is firm to the touch, tender, and often discolored. The abdomen may be significantly discolored and be either plethoric or cyanotic. The clinical presentation of testicular torsion is similar to other scrotal abnormalities, such as hydrocele, inguinal hernia, and trauma; however, it can often be distinguished due to the presence of scrotal discoloration and an inability to be transilluminated. Information related to testicular blood flow can be obtained via the use of color Doppler ultrasound. Because of the emergent need for surgical intervention, the diagnosis of testicular torsion must be considered in all infants presenting with scrotal swelling.

Collaborative Management

Treatment of acute testicular torsion is immediate surgery to untwist the testicle and restore blood supply. Timing of the intervention is critical, and a delay in surgical intervention of 4 to 6 hours following initiation of symptoms offers little to no chance of testicular survival. If the torsion occurs antenatally, the chance for testicular survival is nearly nonexistent, and surgical intervention may be futile (Basta et al., 2015). The most important determinant in the decision to perform surgery is the appearance of the scrotum in the delivery room. If the scrotum appears normal initially and then becomes acutely painful, swollen, and discolored, immediate surgery is indicated in an attempt to salvage the testicle. If the scrotum appears blue, hard, and painless immediately after birth, the torsion occurred prenatally and the testicle has already become necrotic.

Controversy exists regarding the treatment of antenatally occurring testicular torsion. Some advocate conservative treatment with regular ultrasound examination to monitor for testicular atrophy. Others suggest contralateral orchiopexy is necessary to prevent the possibility of torsion and subsequent necrosis of both testes (Nandi & Murphy, 2011).

Nursing Management

The focus of nursing care is on keeping the infant as comfortable and quiet as possible. The abdominal girth should be measured every 4 hours to assess for distention. The infant should be positioned supine with head turned to the side or in a side-lying position to avoid excessive pressure on the abdominal and scrotal areas.

If surgery is required, nursing care is centered on the stability of the vital signs and prevention of infection. The suture line is generally small but still requires aseptic technique. The site should be assessed for edema, drainage, or discoloration.

NEPHROBLASTOMA (WILMS' TUMOR)

Pathophysiology

Wilms' tumor (nephroblastoma) is a well-encapsulated heterogeneous malignant tumor of the kidney. It is thought to be due to persistent nephrogenic embryological cells that fail to develop appropriately. Wilms' tumor is associated with other anomalies, including aniridia (lack of development or absence of the iris), GU tract anomalies, and Beckwith–Wiedemann syndrome (Style et al., 2018).

Risk Factors

The incidence of Wilms' tumor in neonates is rare, with the incidence increasing as the infant ages. It can be detected prenatally (Toussi, Granberg, & Gargollo, 2018). Wilms' tumor is generally a sporadic condition, but 1% of those affected have a family history of the disease (Powis, 2010; van den Heuvel-Eibrink et al., 2017).

Clinical Manifestations

The typical presentation of Wilms' tumor is a unilateral smooth, solid abdominal or flank mass that does not cross the midline in an otherwise well-appearing infant (Powis, 2010). Microscopic hematuria may be present, and HTN may occur if associated renal artery stenosis or increased renin secretion is present (Leclair et al., 2005).

Diagnosis

Prenatal diagnosis is uncommon, and most are diagnosed after birth (Toussi et al., 2018). Prenatally, Wilms' tumor is associated with an increased risk of fetal distress, hydrops, and prematurity (Leclair et al., 2005). Postnatally, the initial diagnostic procedure is an abdominal ultrasound to determine the origin of the abdominal mass. Either CT or MRI generally follows the ultrasound to make a definitive diagnosis and to determine the cancer stage (Powis, 2010). Biopsies are usually unnecessary in infants under 6 months of age.

Prognosis

Prognosis is related to the stage of disease and size of the tumor. Children younger than 2 years generally have a very favorable prognosis, but the risk of complications is higher in neonates (Toussi et al., 2018).

Collaborative Management

Because of the possibility that the encapsulated tumor may rupture and seed other areas of the body, repeated abdominal examinations should be avoided. Treatment of unilateral Wilms' tumor generally includes only nephroureterectomy in the neonate. If the tumor is bilateral, if shrinkage is necessary prior to removal, or if metastasis has occurred, chemotherapy may be required (van den Heuvel-Eibrink et al., 2017). **Quality and Safety: The diagnosis of cancer in a young infant can be devastating to the family. Clear, easy-to-understand information related to treatment and prognosis is required to assist parents to have realistic expectations related to their infant's diagnosis.**

SUMMARY

The infant with a GU abnormality presents unique challenges to the neonatal care team. Although aberrations in the genital system are not life-threatening, their appearance can be traumatic for parents. Urinary tract pathology, on the other hand, can result in emergent life-threatening events at any age. Renal abnormality and diseases manifesting in the neonatal period can have lifelong consequences. The neonatal nurse must be able to accurately assess and respond to alterations in renal function. Astute nursing care of the infant and parents is paramount to optimal management and outcome. The neonatal nurse is in the position to be the first member of the healthcare team to detect minor changes in neonatal physiological functions that may signify onset of significant compromise. To do this, the neonatal nurse must have knowledge of normal and abnormal renal and urinary tract physiology and pathophysiology. Parental support is another aspect of nursing care that is of major importance when caring for the infant with GU conditions. Timely assessment of parental coping mechanisms, alterations in parent–infant attachment, and evaluation of the parents' response to teaching provide vital information that will ultimately affect the infant's overall well-being.

CASE STUDY

■ **Identification of the Problem.** Infant with an average urinary output of 0.4 mL/kg/hour for the past 24 hours.

■ **Assessment: History and Physical Examination.** The child is a 3-day-old, 900-g, 28-week of gestational age infant born to a 28-year-old gravida 1, para 0 mother. Blood type is A+, and all serologies including Venereal Disease Research Laboratory (VDRL), HbsAg, GC, and HIV are negative. The mother received good prenatal care during this pregnancy. No smoking, drug, or alcohol use reported. Delivery was via cesarean birth due to placental abruption at 28 weeks' gestation. No antibiotics or prenatal steroids were administered prior to delivery. Infant required intubation at delivery because of apnea and low heart rate. Apgar scores were 4 at 1 minute and 8 at 5 minutes. Infant was transferred to the Level 3 NICU. His problems included the following:

- Fluid, electrolytes, and nutrition: He is currently on minimal enteral feedings of 1 mL every 12 hours and tolerating these well; his total fluid volume is 120 mL/kg/day of total parenteral nutrition.
- Respiratory: He received two doses of surfactant for a chest radiograph consistent with hyaline membrane disease; he remains intubated on moderate ventilatory settings.
- Cardiovascular: Infant has had several episodes of hypotension that have resolved spontaneously without treatment; heart rate is 175; current blood pressure has a mean arterial pressure of 28.
- Infectious disease; receiving ampicillin and gentamicin for suspected sepsis; no culture-proven sepsis.
- Hematologic: Hematocrit is 35%; under phototherapy for hyperbilirubinemia.
- Neurologic: A cranial ultrasound has been ordered for 1 week of life.
- Social: Parents are married; this is their first child; they are appropriately concerned and have been updated at the bedside daily.

■ **Physical Assessment**

- GENERAL: no obvious anomalies noted
- HEENT: anterior fontanelle soft and flat; eyes clear without drainage, red reflex present; pupils equally reactive to light; nares patent bilaterally; no clefts or abnormalities of mouth noted; ear canals patent bilaterally
- CHEST AND LUNGS: heart rate regular without murmur; pulses equal in all four extremities; quiet precordium; capillary refill time is 2 seconds; lungs equal with fine crackles bilaterally
- ABDOMEN: soft and nondistended; positive bowel sounds auscultated in all four quadrants; no masses felt; umbilical cord normal; liver felt 2 cm below right intercostal margin
- GU: normal female infant; genitalia appropriate for gestational age
- SKELETAL: moves all extremities well; no obvious anomalies noted
- NEUROLOGIC: all reflexes present; tone appropriate for gestational age

■ **Differential Diagnoses.** The differential diagnosis of oliguria in this infant includes:

- Prerenal failure associated with decreased renal blood due to low systemic blood pressure or inadequate fluid intake
- Intrinsic renal failure due to the administration of nephrotoxic medications (gentamicin) or ATN due to perinatal depression related to the placental abruption as evidenced by the low Apgar scores
- Postrenal obstruction due to a neurogenic bladder related to fentanyl administration

■ **Diagnostic Tests.** Palpate the abdomen for the presence of a distended bladder and perform an in-and-out catheterization.

- Electrolytes: sodium 148; potassium 3.5; creatinine 0.4; BUN 10
- Weight is 780 g
- Gentamicin trough is 0.4 mg/L
- Urine specific gravity is 1,020, no protein, blood, or WBCs are present in the urine

The next step should be administration of 10 to 20 mL/kg of normal saline via IV. Use of a diuretic after the fluid challenge may be necessary if urine output does not increase immediately after the fluid challenge.

■ **Working Diagnosis.** The bladder is not distended. No urine is obtained via in-and-out catheterization, thus ruling out postrenal failure.

Physical assessment is imperative for lack of abdominal masses that would possibly indicate an enlarged kidney and associated intrinsic renal failure. Tachycardia is present, possibly indicating mild dehydration. A borderline mean arterial pressure may indicate decreased intravascular volume or decreased systemic blood flow.

Infant has lost 120 g over the past 3 days.

Gentamicin level is normal and does not support the presence of intrinsic renal failure.

The sodium level and specific gravity are elevated, which are both consistent with prerenal failure.

The creatinine and BUN levels are normal. If elevated, they would support a diagnosis of intrinsic renal failure.

There is no blood or protein in the urine. The presence of these substances would also support a diagnosis of intrinsic renal failure.

The administration of a fluid challenge produced a urine output of over 1 mL/kg/hour, thus indicating a diagnosis of prerenal failure.

No other workup, such as a renal ultrasound, would be indicated at this time.

■ **Development of Management Plan.** Ensure administration of an adequate fluid volume by increasing fluid volume appropriately to ensure a urine output over 1 mL/kg/hour. Compensate for fluid losses due to insensible water losses, including losses from phototherapy.

Low-dose dopamine may increase renal blood flow.

Ensure appropriate renal blood flow by increasing mean arterial pressure. If increase in fluid volume does not increase blood pressure sufficiently, inotropes such as higher dose dopamine or dobutamine may be administered.

■ **Implementation and Evaluation of Effectiveness**

Monitor skin turgor and fontanelles for signs of dehydration.

- Monitor serum electrolytes closely to ensure normalization of sodium levels
- Monitor vital signs every 3 to 4 hours to ensure normalization of blood pressure and heart rate
- Carefully monitor intake and output to ensure that infant is receiving adequate volume to result in a urine output of over 1 mL/kg/hour
- Daily or twice-daily weights
- Monitor specific gravity to ensure resolution to a normal range

EVIDENCE-BASED PRACTICE BOX

UTIs are common in infants and are defined as infection of the kidney and/or the bladder. They are estimated to occur in 0.1% to 2% of all newborns and in 20% of preterm and critically ill infants. UTIs can increase morbidity and, if not properly treated, can result in decreased renal function, renal scarring, and hypertension (Arshad & Seed, 2015). Treatment of UTIs consists of antibiotic therapy, and traditionally due to concerns of VUR, a VCUG and prophylactic antibiotic therapy were recommended in all infants diagnosed with a UTI. Unfortunately, a VCUG is not a benign procedure and is associated with both infant pain and family stress.

Evidence now exists that the risk of recurrent UTI is not significantly affected by VUR, and the AAP currently recommends that a VCUG not be performed following the first UTI unless the renal ultrasound indicates abnormalities including hydronephrosis, renal scarring, severe VUR, or obstructive uropathy (Roberts et al., 2011). A meta-analysis of six studies including data on 1,091 infants indicated no benefit in providing prophylactic antibiotics to prevent future UTIs in infants with grades I to IV VUR, and there was insufficient data regarding use in infants with grade V VUR (Roberts et al., 2011). Furthermore, it is estimated that only 1% of infants diagnosed with a UTI has grade V VUR (Roberts et al., 2011). Therefore, the use of a VCUG or prophylactic antibiotic therapy is not recommended following an initial UTI (Roberts et al., 2011). If an infant is diagnosed with subsequent UTIs, a VCUG is required at that time (Roberts et al., 2011).

References

Arshad, M., & Seed, P. C. (2015). Urinary tract infections in the infant. *Clinics in Perinatology, 42*(1), 17–28. doi:10.1016/j.clp.2014.10.003

Roberts, K. B., Downs, S. M., Finnell, S. M. E., Hellerstein, S., Shortliffe, L. D., Wald, E. R., & Zerin, J. M. (2011). Urinary tract infection: Clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. *Pediatrics, 128*(3), 595–610. doi:10.1542/peds.2011-1330

ONLINE RESOURCES

American Urological Association Foundation. Retrieved from http://www.auanet.org

International Pediatric Endosurgery Group Guidelines for Inguinal Hernias and Hydroceles. Retrieved from https://www.ipeg.org/hernia

Lannon, C. M., Bailey, A. G. D., Fleischman, A. R., Kaplan, G. W., Shoemaker, C. T., Swanson, J. T., & Coustan, D. (2012). Circumcision policy statment. *Pediatrics, 103*(3), 585. doi:10.1542/peds.2012-1989

The National Kidney Foundation. Retrieved from http://www.kidney.org

National Kidney and Urologic Diseases Information Clearinghouse. A service of the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health. Retrieved from https://www.niddk.nih.gov/

REFERENCES

Abitbol, C. L., Seeherunvong, W., Galarza, M. G., Katsoufis, C., Francoeur, D., Defreitas, M., & Zilleruelo, G. (2014). Neonatal kidney size and function in preterm infants: What is a true estimate of glomerular filtration rate? *Journal of Pediatrics, 164*(5), 1026–1031. e1022. doi:10.1016/j.jpeds.2014.01.044

Albero, G., Castellsague, X., Giuliano, A. R., & Bosch, F. X. (2012). Male circumcision and genital human papillomavirus: A systematic review and meta-analysis. *Sexually Transmitted Diseases, 39*(2), 104–113. doi:10.1097/OLQ.0b013e3182387abd

American Cancer Society. (2017). Can penile cancer be prevented? Retrieved from https://www.cancer.org/cancer/penilecancer/detailedguide/penile-cancer-prevention

Arlen, A. M., Kirsch, S. S., Seidel, N. E., Garcia-Roig, M., Smith, E. A., & Kirsch, A. J. (2016). Health-related quality of life in children with prune-belly syndrome and their caregivers. *Urology, 87*, 224–227. doi:10.1016/j.urology.2015.09.028

Arshad, M., & Seed, P. C. (2015). Urinary tract infections in the infant. *Clinics in Perinatology, 42*(1), 17–28. doi:10.1016/j.clp.2014.10.003

Basta, A. M., Courtier, J., Phelps, A., Copp, H. L., & MacKenzie, J. D. (2015). Scrotal swelling in the neonate. *Journal of Ultrasound in Medicine, 34*(3), 495–505. doi:10.7863/ultra.34.3.495

Baum, M. (2015). Overview of polycystic kidney disease in children. *Current Opinion in Pediatrics, 27*(2), 184–185. doi:10.1097/mop.0000000000000198

Bidadi, B., Nageswara Rao, A. A., Kaur, D., Khan, S. P., & Rodriguez, V. (2016). Neonatal renal vein thrombosis: Role of anticoagulation and thrombolysis—An institutional review. *Pediatric Hematology and Oncology, 33*(1), 59–66. doi:10.3109/08880018.2015.1132801

Blackburn, S. T. (2013). *Maternal, fetal, and neonatal physiology: A clinical perspective* (4th ed.). St. Louis, MO: Elsevier Saunders.

Boer, D. P., de Rijke, Y. B., Hop, W. C., Carnsberg, K., & Dorresteijn, E. M. (2010). Reference values for serum creatinine in children younger than 1 year of age. *Pediatric Nephrology, 25*, 2107–2111.

Bonadio, W., & Maida, G. (2014). Urinary tract infection in outpatient febrile infants younger than 30 days of age: A 10-year evaluation. *Pediatric Infectious Disease Journal, 33*(4), 342–344. doi:10.1097/inf.0000000000000110

Bonilla-Felix, M. (2017). Potassium regulation in the neonate. *Pediatric Nephrology, 32*(11), 2037–2049. doi:10.1007/s00467-017-3635-2

Brandao, L. R., Simpson, E. A., & Lau, K. K. (2011). Neonatal renal vein thrombosis. *Seminars in Fetal and Neonatal Medicine, 16*(6), 323–328. doi:10.1016/j.siny.2011.08.004

Caione, P., & Nappo, S. G. (2011). Posterior urethral valves: Long-term outcome. *Pediatric Surgery International, 27*(10), 1027–1035. doi:10.1007/s00383-011-2946-9

Casella, D. P., Tomaszewski, J. J., & Ost, M. C. (2012). Posterior urethral valves: Renal failure and prenatal treatment. *International Journal of Nephrology, 2012*, 351067. doi:10.1155/2012/351067

Cavaliere, T. A. (2019). Genitourinary assessment. In E. D. Tappero & M. E. Honeyfield (Eds.), *Physical assessment of the newborn: A comprehensive approach to the art of physical examination* (6th ed.). New York, NY: Springer Publishing Company.

Chevalier, R. L. (2004). Perinatal obstructive nephropathy. *Seminars in Perinatology, 28*, 124–131. doi:10.1053/j.semperi.2003.11.009

Chiappinelli, A., Savanelli, A., Farina, A., & Settimi, A. (2011). Multicystic dysplastic kidney: Our experience in non-surgical management. *Pediatric Surgery International, 27*(7), 775–779. doi:10.1007/s00383-011-2910-8

Chock, V. Y., Frymoyer, A., Yeh, C. G., & Van Meurs, K. P. (2018). Renal saturation and acute kidney injury in neonates with hypoxic ischemic encephalopathy undergoing therapeutic hypothermia. *Journal of Pediatrics, 200*, 232–239.e1. doi:10.1016/j.jpeds.2018.04.076

Choi, Y. H., Cheon, J.-E., Kim, W. S., & Kim, I.-O. (2016). Ultrasonography of hydronephrosis in the newborn: A practical review. *Ultrasonography, 35*(3), 198–211. doi:10.14366/usg.15073

Clark, D. (2000). *Atlas of neonatology*. Philadelphia, PA: Saunders.

Clayton, D. B., & Brock, J. W. (2018). Current state of fetal intervention for lower urinary tract obstruction. *Current Urology Reports, 19*(1), 12. doi:10.1007/s11934-018-0760-9

Coulthard, M. G. (2016). The management of neonatal acute and chronic renal failure: A review. *Early Human Development, 102*, 25–29. doi:10.1016/j.earlhumdev.2016.09.004

Davidovits, M., Cleper, R., Eizenberg, N., Hocherman, O., & Mashiach, R. (2017). Outcomes of prenatally diagnosed solitary functioning kidney during early life. *Journal of Perinatology, 37*(12), 1325–1329. doi:10.1038/jp.2017.143

de Boom, M. L., Kist-van Holthe, J. E., Sramek, A., Lardenoye, S. W., Walther, F. J., & Loprior, E. (2010). Is screening for renal anomalies warranted in neonates with isolated umbilical artery? *Neonatology, 97*, 225–227.

Dell, K. M. (2011). The spectrum of polycystic kidney disease in children. *Advances in Chronic Kidney Disease, 18*(5), 339–347. doi:10.1053/j.ackd.2011.05.001

Dias, T., Sairam, S., & Kumarasiri, S. (2014). Ultrasound diagnosis of fetal renal abnormalities. *Best Practice & Research: Clinical Obstetrics & Gynaecology, 28*(3), 403–415. doi:10.1016/j.bpobgyn.2014.01.009

Di Renzo, D., Persico, A., Di Nicola, M., Silvaroli, S., Martino, G., & LelliChiesa, P. (2015). Conservative management of primary non-refluxing megaureter during the first year of life: A longitudinal observational study. *Journal of Pediatric Urology, 11*(4), 226.e1–226.e6. doi:10.1016/j.jpurol.2015.05.007

Ek, S., Lidefeldt, K. J., & Varricio, L. (2007). Fetal hydronephrosis; prevalence, natural history and postnatal consequences in an unselected population. *Acta Obstetricia et Gynecologica Scandinavica, 86*(12), 1463–1466. doi:10.1080/00016340701714802

El Bcheraoui, C., Zhang, X., Cooper, C. S., Rose, C. E., Kilmarx, P. H., & Chen, R. T. (2014). Rates of adverse events associated with male circumcision in U.S. medical settings, 2001 to 2010. *JAMA Pediatrics, 168*(7), 625–634. doi:10.1001/jamapediatrics.2013.5414

Epelman, M., Victoria, T., Meyers, K. E., Chauvin, N., Servaes, S., & Darge, K. (2012). Postnatal imaging of neonates with prenatally diagnosed genitourinary abnormalities: A practical approach. *Pediatric Radiology, 42*(Suppl. 1), S124–S141. doi:10.1007/s00247-011-2177-1

Filler, G., Guerrero-Kanan, R., & Alvarez-Elias, A. C. (2016). Assessment of glomerular filtration rate in the neonate: Is creatinine the best tool? *Current Opinion in Pediatrics, 28*(2), 173–179. doi:10.1097/mop.0000000000000318

Flannery, D. D., Brandsma, E., Saslow, J., Mackley, A. B., Paul, D. A., & Aghai, Z. H. (2017). Do infants in the neonatal intensive care unit diagnosed with urinary tract infection need a routine voiding cystourethrogram? *Journal of Maternal-Fetal & Neonatal Medicine*, 32(4), 1–121. doi:10.1080/14767058.2017.1416352

Garcia-Roig, M. L., Grattan-Smith, J. D., Arlen, A. M., Smith, E. A., & Kirsch, A. J. (2016). Detailed evaluation of the upper urinary tract in patients with prune belly syndrome using magnetic resonance urography. *Journal of Pediatric Urology, 12*(2), 122.e1–122.e7. doi:10.1016/j.jpurol.2015.11.008

Girardi, A., Raschi, E., Galletti, S., Allegaert, K., Poluzzi, E., & De Ponti, F. (2017). Drug-induced renal injury in neonates: Challenges in clinical

practice and perspectives in drug development. *Expert Opinion on Drug Metabolism & Toxicology, 13*(5), 555–565. doi:10.1080/17425255.2017.1290081

Goyal, A., Fishwick, J., Hurrell, R., Cervellione, R. M., & Dickson, A. P. (2012). Antenatal diagnosis of bladder/cloacal exstrophy: Challenges and possible solutions. *Journal of Pediatric Urology, 8*(2), 140–144. doi:10.1016/j.jpurol.2011.05.003

Gubhaju, L., Sutherland, M. R., & Black, M. J. (2011). Preterm birth and the kidney: Implications for long-term renal health. *Reproductive Sciences, 18*(4), 322–333. doi:10.1177/1933719111401659

Gulack, B. C., Greenberg, R., Clark, R. H., Miranda, M. L., Blakely, M. L., Rice, H. E., . . . Smith, P. B. (2018). A multi-institution analysis of predictors of timing of inguinal hernia repair among premature infants. *Journal of Pediatric Surgery, 53*(4), 784–788. doi:10.1016/j.jpedsurg.2017.09.009

Guyton, A. C., & Hall, J. E. (1997). *Human physiology and mechanisms of disease* (6th ed.). Philadelphia, PA: Saunders.

Hanna, M. H., Askenazi, D. J., & Selewski, D. T. (2016). Drug-induced acute kidney injury in neonates. *Current Opinion in Pediatrics, 28*(2), 180–187. doi:10.1097/mop.0000000000000311

Harer, M. W., Pope, C. F., Conaway, M. R., & Charlton, J. R. (2017). Follow-up of acute kidney injury in neonates during childhood years (FANCY): A prospective cohort study. *Pediatric Nephrology, 32*(6), 1067–1076. doi:10.1007/s00467-017-3603-x

Hassett, S., Smith, G. H., & Holland, A. J. (2012). Prune belly syndrome. *Pediatric Surgery International, 28*(3), 219–228. doi:10.1007/s00383-011-3046-6

Herman, T. E., & Siegel, M. J. (2009). Prune belly syndrome. *Journal of Perinatology, 29*(1), 69–71. doi:10.1038/jp.2008.88

Ho, I. G., Ihn, K., Koo, E.-J., Chang, E. Y., & Oh, J.-T. (2018). Laparoscopic repair of inguinal hernia in infants: Comparison with open hernia repair. *Journal of Pediatric Surgery, 53*(10), 2008–2012. doi:10.1016/j.jpedsurg.2018.01.022

Hockenberry, M. J., Wilson, D., Winkelstein, M. L., & Wong, D. L. (Eds.). (2003). *Wong's nursing care of infants and children* (7th ed.). St. Louis, MO: Mosby.

Hoyer, P. F. (2015). Clinical manifestations of autosomal recessive polycystic kidney disease. *Current Opinion in Pediatrics, 27*(2), 186–192. doi:10.1097/mop.0000000000000196

Hwang, J. Y., Shin, J. H., Lee, Y. J., Yoon, H. M., Cho, Y. A., & Kim, K. S. (2018). Percutaneous nephrostomy placement in infants and young children. *Diagnostic and Interventional Imaging, 99*(3), 157–162. doi:10.1016/j.diii.2017.07.002

Inouye, B. M., Purves, J. T., Routh, J. C., Maruf, M., Friedlander, D., Jayman, J., & Gearhart, J. P. (2018). How to close classic bladder exstrophy: Are subspecialty training and technique important? *Journal of Pediatric Urology, 14*(5), 426.e1–426.e6. doi:10.1016/j.jpurol.2018.02.025

Introcaso, C. E., Xu, F., Kilmarx, P. H., Zaidi, A., & Markowitz, L. E. (2013). Prevalence of circumcision among men and boys aged 14 to 59 years in the United States, National Health and Nutrition Examination Surveys 2005–2010. *Sexually Transmitted Diseases, 40*(7), 521–525. doi:10.1097/01.OLQ.0000430797.56499.0d

Jetton, J. G., & Askenazi, D. J. (2014). Acute kidney injury in the neonate. *Clinics in Perinatology, 41*(3), 487–502. doi:10.1016/j.clp.2014.05.001

Jetton, J. G., & Sorenson, M. (2017). Pharmacological management of acute kidney injury and chronic kidney disease in neonates. *Seminars in Fetal and Neonatal Medicine, 22*(2), 109–115. doi:10.1016/j.siny.2016.09.002

Jnah, A. J., & Trembath, A. N. (Eds.). (2019). *Fetal and neonatal physiology for the advanced practice nurse*. New York, NY: Springer Publishing Company.

John, C. M., Kooner, G., Mathew, D. E., Ahmed, S., & Kenny, S. E. (2008). Neonatal testicular torsion—A lost cause? *Acta Paediatrica, 97*(4), 502–504. doi:10.1111/j.1651-2227.2008.00701.x

Joseph, C., & Gattineni, J. (2016). Proteinuria and hematuria in the neonate. *Current Opinion in Pediatrics, 28*(2), 202–208. doi:10.1097/mop.0000000000000323

Kastl, J. T. (2017). Renal function in the fetus and neonate—The creatinine enigma. *Seminars in Fetal and Neonatal Medicine, 22*(2), 83–89. doi:10.1016/j.siny.2016.12.002

Kibar, Y., Ashley, R. A., Roth, C. C., Frimberger, D., & Kropp, B. P. (2011). Timing of posterior urethral valve diagnosis and its impact on clinical outcome. *Journal of Pediatric Urology, 7*(5), 538–542. doi:10.1016/j.jpurol.2010.08.002

Koeppen, B., & Stanton, B. (2013). *Renal physiology* (5th ed.). St. Louis, MO: Mosby.

Kolon, T. F., Herndon, C. D., Baker, L. A., Baskin, L. S., Baxter, C. G., Cheng, E. Y., . . . Barthold, J. S. (2014). Evaluation and treatment of cryptorchidism: AUA guideline. *Journal of Urology, 192*(2), 337–345. doi:10.1016/j.juro.2014.05.005

Kraft, J. K., Brandao, L. R., & Navarro, O. M. (2011). Sonography of renal venous thrombosis in neonates and infants: Can we predict outcome? *Pediatric Radiology, 41*(3), 299–307. doi:10.1007/s00247-010-1817-1

Krill, A. J., Palmer, L. S., & Palmer, J. S. (2011). Complications of circumcision. *Scientific World Journal, 11*, 2458–2468. doi:10.1100/2011/373829

Lang, E. K., Allaei, A., Robinson, L., Reid, J., & Zinn, H. (2015). Minimally invasive radiologic techniques in the treatment of ureteroenteric fistulas. *Diagnostic and Interventional Imaging, 96*(11), 1153–1160. doi:10.1016/j.diii.2015.06.010

Lannon, C. M., Bailey, A. G. D., Fleischman, A. R., Kaplan, G. W., Shoemaker, C. T., Swanson, J. T., & Coustan, D. (2012). Circumcision policy statement. *Pediatrics, 103*(3), 585. doi:10.1542/peds.2012-1989

Lao, O. B., Fitzgibbons, R. J., Jr., & Cusick, R. A. (2012). Pediatric inguinal hernias, hydroceles, and undescended testicles. *Surgical Clinics of North America, 92*(3), 487–504. doi:10.1016/j.suc.2012.03.017

Larke, N. L., Thomas, S. L., dos Santos Silva, I., & Weiss, H. A. (2011). Male circumcision and penile cancer: A systematic review and meta-analysis. *Cancer Causes Control, 22*(8), 1097–1110. doi:10.1007/s10552-011-9785-9

Lau, K. K., Stoffman, J. M., Williams, S., McCusker, P., Brandao, L., Patel, S., & Chan, A. K. (2007). Neonatal renal vein thrombosis: Review of the English-language literature between 1992 and 2006. *Pediatrics, 120*(5), e1278–e1284. doi:10.1542/peds.2007-0510

Leclair, M. D., El-Ghoneimi, A., Audry, G., Ravasse, P., Moscovici, J., & Heloury, Y. (2005). The outcome of prenatally diagnosed renal tumors. *Journal of Urology, 173*(1), 186–189. doi:10.1097/01.ju.0000147300.53837.8f

Lee, C.-C., Chan, O.-W., Lai, M.-Y., Hsu, K.-H., Wu, T.-W., Lim, W.-H., . . . Lien, R. (2017). Incidence and outcomes of acute kidney injury in extremely-low-birth-weight infants. *PLoS One, 12*(11), e0187764. doi:10.1371/journal.pone.0187764

Leeners, B., Sauer, I., Schefels, J., Cotarelo, C. L., & Funk, A. (2000). Prune-belly syndrome: Therapeutic options including in utero placement of a vesicoamniotic shunt. *Journal of Clinical Ultrasound, 28*(9), 500–507. doi:10.1002/1097-0096(200011/12)28:9<500::AID-JCU10>3.0.CO;2-8

Lei, J. H., Liu, L. R., Wei, Q., Yan, S. B., Yang, L., Song, T. R., . . . Han, P. (2015). Circumcision status and risk of HIV acquisition during heterosexual intercourse for both males and females: A meta-analysis. *PLoS One, 10*(5), e0125436. doi:10.1371/journal.pone.0125436

Lloyd, J. C., Wiener, J. S., Gargollo, P. C., Inman, B. A., Ross, S. S., & Routh, J. C. (2013). Contemporary epidemiological trends in complex congenital genitourinary anomalies. *Journal of Urology, 190*(4, Suppl.), 1590–1595. doi:10.1016/j.juro.2013.04.034

Luo, X., Zhai, S., Shi, N., Li, M., Cui, S., Xu, Y., . . . Liu, R. (2017). The risk factors and neonatal outcomes of isolated single umbilical artery in singleton pregnancy: A meta-analysis. *Scientific Reports, 7*(1), 7396. doi:10.1038/s41598-017-07053-7

Luyckx, V. A., & Brenner, B. M. (2010). The clinical importance of nephron mass. *Journal of the American Society of Nephrology, 21*(6), 898–910. doi:10.1681/asn.2009121248

Mao, Y., Francis-West, P., & Irvine, K. D. (2015). Fat4/Dchs1 signaling between stromal and cap mesenchyme cells influences nephrogenesis and ureteric bud branching. *Development, 142*(15), 2574–2585. doi:10.1242/dev.122630

Maqsood, S., Fung, N., Chowdhary, V., Raina, R., & Mhanna, M. J. (2017). Outcome of extremely low birth weight infants with a history of neonatal acute kidney injury. *Pediatric Nephrology, 32*(6), 1035–1043. doi:10.1007/s00467-017-3582-y

Marlais, M., Cuthell, O., Langan, D., Dudley, J., Sinha, M. D., & Winyard, P. J. (2016). Hypertension in autosomal dominant polycystic kidney disease: A meta-analysis. *Archives of Disease in Childhood, 101*(12), 1142–1147. doi:10.1136/archdischild-2015-310221

Misurac, J. (2017). Chronic kidney disease in the neonate: Etiologies, management, and outcomes. *Seminars in Fetal and Neonatal Medicine, 22*(2), 98–103. doi:10.1016/j.siny.2016.09.003

Moore, K. L., Persaud, T. V. N., & Torchia, M. G. (2016). *The developing human: Clinically oriented embryology* (10th ed.). Philadelphia, PA: Elsevier Saunders.

Morris, B. J., Kennedy, S. E., Wodak, A. D., Mindel, A., Golovsky, D., Schrieber, L., . . . Ziegler, J. B. (2017). Early infant male circumcision: Systematic review, risk-benefit analysis, and progress in policy. *World Journal of Clinical Pediatrics, 6*(1), 89–102. doi:10.5409/wjcp.v6.i1.89

Morris, B. J., & Wiswell, T. E. (2013). Circumcision and lifetime risk of urinary tract infection: A systematic review and meta-analysis. *Journal of Urology, 189*(6), 2118–2124. doi:10.1016/j.juro.2012.11.114

Morris, R. K., Malin, G. L., Khan, K. S., & Kilby, M. D. (2010). Systematic review of the effectiveness of antenatal intervention for the treatment of congenital lower urinary tract obstruction. *British Journal of Obstetrics and Gynecology, 117*(4), 382–390. doi:10.1111/j.1471-0528.2010.02500.x

Morris, R. K., Middleton, L. J., Malin, G. L., Quinlan-Jones, E., Daniels, J., Khan, K. S., . . . Kilby, M. D. (2015). Outcome in fetal lower urinary tract obstruction: A prospective registry study. *Ultrasound in Obstetrics & Gynecology, 46*(4), 424–431. doi:10.1002/uog.14808

Nada, A., Bonachea, E. M., & Askenazi, D. J. (2017). Acute kidney injury in the fetus and neonate. *Seminars in Fetal and Neonatal Medicine, 22*(2), 90–97. doi:10.1016/j.siny.2016.12.001

Nandi, B., & Murphy, F. L. (2011). Neonatal testicular torsion: A systematic literature review. *Pediatric Surgery International, 27*(10), 1037–1040. doi:10.1007/s00383-011-2945-x

Nasir, A. A., Ameh, E. A., Abdur-Rahman, L. O., Adeniran, J. O., & Abraham, M. K. (2011). Posterior urethral valve. *World Journal of Pediatrics, 7*(3), 205–216. doi:10.1007/s12519-011-0289-1

Nassr, A. A., Shazly, S. A. M., Abdelmagied, A. M., Araujo Júnior, E., Tonni, G., Kilby, M. D., & Ruano, R. (2017). Effectiveness of vesicoamniotic shunt in fetuses with congenital lower urinary tract obstruction: An updated systematic review and meta-analysis. *Ultrasound in Obstetrics & Gynecology, 49*(6), 696–703. doi:10.1002/uog.15988

Nelson, R. (2015). New CDC guidelines recommend circumcision to cut HIV risk. *The Lancet Infectious Diseases, 15*(3), 269–270. doi:10.1016/s1473-3099(15)70071-x

Nguyen, H. T., Herndon, C. D., Cooper, C., Gatti, J., Kirsch, A., Kokorowski, P., . . . Campbell, J. B. (2010). The Society for Fetal Urology consensus statement on the evaluation and management of antenatal hydronephrosis. *Journal of Pediatric Urology, 6*(3), 212–231. doi:10.1016/j.jpurol.2010.02.205

O'Conner-Von, S., & Turner, H. N. (2013). American Society for Pain Management Nursing (ASPMN) position statement: Male infant circumcision pain management. *Pain Management Nursing, 14*(4), 379–382. doi:10.1016/j.pmn.2011.08.007

Odeh, R., Noone, D., Bowlin, P. R., Braga, L. H., & Lorenzo, A. J. (2016). Predicting risk of chronic kidney disease in infants and young children at diagnosis of posterior urethral valves: Initial ultrasound kidney characteristics and validation of parenchymal area as forecasters of renal reserve. *Journal of Urology, 196*(3), 862–868. doi:10.1016/j.juro.2016.03.137

O'Kelly, F., Keefe, D., Herschorn, S., & Lorenzo, A. J. (2018). Contemporary issues relating to transitional care in bladder exstrophy. *Canadian Urological Association Journal, 12*(4, Suppl. 1), S15–S23. doi:10.5489/cuaj.5313

Oliveira, E. A., Oliveira, M. C., & Mak, R. H. (2016). Evaluation and management of hydronephrosis in the neonate. *Current Opinion in Pediatrics, 28*(2), 195–201. doi:10.1097/mop.0000000000000321

Papantoniou, N., Papoutsis, D., Daskalakis, G., Chatzipapas, I., Sindos, M., Papaspyrou, I., . . . Antsaklis, A. (2010). Prenatal diagnosis of prune-belly syndrome at 13 weeks of gestation: Case report and review of literature. *Journal of Maternal-Fetal and Neonatal Medicine, 23*(10), 1263–1267. doi:10.3109/14767050903544777

Phua, Y. L., & Ho, J. (2016). Renal dysplasia in the neonate. *Current Opinion in Pediatrics, 28*(2), 209–215. doi:10.1097/mop.0000000000000324

Pierre, K., Borer, J., Phelps, A., & Chow, J. S. (2014). Bladder exstrophy: Current management and postoperative imaging. *Pediatric Radiology, 44*(7), 768–786; quiz 765–767. doi:10.1007/s00247-014-2892-5

Powis, M. (2010). Neonatal renal tumours. *Early Human Development, 86*(10), 607–612. doi:10.1016/j.earlhumdev.2010.08.018

Purdy, I. B., Craig, J. W., & Zeanah, P. (2015). NICU discharge planning and beyond: Recommendations for parent psychosocial support. *Journal of Perinatology, 35*(Suppl. 1), S24–S28. doi:10.1038/jp.2015.146

Rees, L. (2017). Renal replacement therapies in neonates: Issues and ethics. *Seminars in Fetal and Neonatal Medicine, 22*(2), 104–108. doi:10.1016/j.siny.2016.11.001

Reinfeldt Engberg, G., Mantel, A., Fossum, M., & Nordenskjold, A. (2016). Maternal and fetal risk factors for bladder exstrophy: A nationwide Swedish case-control study. *Journal of Pediatric Urology, 12*(5), 304.e1–e7. doi:10.1016/j.jpurol.2016.05.035

Resontoc, L. P., & Yap, H. K. (2016). Renal vascular thrombosis in the newborn. *Pediatric Nephrology, 31*(6), 907–915. doi:10.1007/s00467-015-3160-0

Roberts, K. B., Downs, S. M., Finnell, S. M. E., Hellerstein, S., Shortliffe, L. D., Wald, E. R., Zerin, J. M. (2011). Urinary tract infection: Clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. *Pediatrics, 128*(3), 595–610. doi:10.1542/peds.2011-1330

Sarhan, O. M., Alghanbar, M., Alsulaihim, A., Alharbi, B., Alotay, A., & Nakshabandi, Z. (2014). Multicystic dysplastic kidney: Impact of imaging modality selection on the initial management and prognosis. *Journal of Pediatric Urology, 10*(4), 645–649. doi:10.1016/j.jpurol.2014.03.004

Schoen, E. J., Anderson, G., Bohon, C., Hinman, F., Jr., Poland, R. L., & Wakeman, E. M. (1989). Report of the Task Force on Circumcision. *Pediatrics, 84*(4), 388–391. Retrieved from https://pediatrics.aappublications.org/content/pediatrics/84/2/388.full.pdf

Seidel, N. E., Arlen, A. M., Smith, E. A., & Kirsch, A. J. (2015). Clinical manifestations and management of prune-belly syndrome in a large contemporary pediatric population. *Urology, 85*(1), 211–215. doi:10.1016/j.urology.2014.09.029

Selewski, D. T., Charlton, J. R., Jetton, J. G., Guillet, R., Mhanna, M. J., Askenazi, D. J., & Kent, A. L. (2015). Neonatal acute kidney injury. *Pediatrics, 136*(2), e463–e473. doi:10.1542/peds.2014-3819

Sharma, S. C., Raison, N., Khan, S., Shabbir, M., Dasgupta, P., & Ahmed, K. (2018). Male circumcision for the prevention of human immunodeficiency virus (HIV) acquisition: A meta-analysis. *BJU International, 121*(4), 515–526. doi:10.1111/bju.14102

Siffel, C., Correa, A., Amar, E., Bakker, M. K., Bermejo-Sanchez, E., Bianca, S., . . . Olney, R. S. (2011). Bladder exstrophy: An epidemiologic study from the International Clearinghouse for Birth Defects Surveillance and Research, and an overview of the literature. *American Journal of Medical Genetics. Part C, Seminars in Medical Genetics, 157C*(4), 321–332. doi:10.1002/ajmg.c.30316

Springate, J. E., Fildes, R. D., & Feld, L. G. (1987). Assessment of renal function in newborn infants. *Pediatrics in Review, 9*(2), 51–56. doi:10.1542/pir.9-2-51

Stein, R., Dogan, H. S., Hoebeke, P., Kocvara, R., Nijman, R. J., Radmayr, C., & Tekgul, S. (2015). Urinary tract infections in children: EAU/ESPU guidelines. *European Urology, 67*(3), 546–558. doi:10.1016/j.eururo.2014.11.007

Style, C. C., Cruz, S. M., Lau, P. E., Lee, T. C., Wesson, D. E., & Olutoye, O. O. (2018). Surgical outcomes of patients with Beckwith-Wiedemann syndrome. *Journal of Pediatric Surgery, 53*(5), 1042–1045. doi:10.1016/j.jpedsurg.2018.02.041

Suzuki, K., Matsumaru, D., Matsushita, S., Murashima, A., Ludwig, M., Reutter, H., & Yamada, G. (2017). Epispadias and the associated

embryopathies: Genetic and developmental basis. *Clinical Genetics, 91*(2), 247–253. doi:10.1111/cge.12871

Tappero, E. D., & Honeyfield, M. E. (2019). *Physical assessment of the newborn: A comprehensive approach to the art of physical exam* (6th ed.). New York, NY: Springer Publishing Company.

Tiryaki, S., Alkac, A. Y., Serdaroglu, E., Bak, M., Avanoglu, A., & Ulman, I. (2013). Involution of multicystic dysplastic kidney: Is it predictable? *Journal of Pediatric Urology, 9*(3), 344–347. doi:10.1016/j.jpurol.2012.04.014

Tortora, G. J., & Derrickson, B. (2017). *Principles of anatomy and physiology* (15th ed.). New York, NY: Wiley.

Toussi, A., Granberg, C. F., & Gargollo, P. C. (2018). A case of prenatally diagnosed Wilms tumor managed with laparoscopic nephrectomy. *Urology, 113*, 197–199. doi:10.1016/j.urology.2017.10.045

Tubre, R. W., & Gatti, J. M. (2015). Surgical approaches to pediatric ureteropelvic junction obstruction. *Current Urology Reports, 16*(10), 72. doi:10.1007/s11934-015-0539-1

van den Heuvel-Eibrink, M. M., Hol, J. A., Pritchard-Jones, K., van Tinteren, H., Furtwangler, R., Verschuur, A. C., . . . Graf, N. (2017). Position paper: Rationale for the treatment of Wilms tumour in the UMBRELLA SIOP-RTSG 2016 protocol. *Nature Reviews Urology, 14*(12), 743–752. doi:10.1038/nrurol.2017.163

Vogt, B. A., & Dell, K. M. (2015). The kidney and urinary tract. In R. J. Martin, A. A. Fanaroff, & M. C. Walsh (Eds.), *Neonatal-perinatal medicine: Diseases of the fetus and infant* (10th ed., Vol. 1). St. Louis, Mo: Elsevier Saunders.

Weitz, M., & Schmidt, M. (2017). To screen or not to screen for vesicoureteral reflux in children with ureteropelvic junction obstruction: A systematic review. *European Journal of Pediatrics, 176*(1), 1–9. doi:10.1007/s00431-016-2818-3

Winding, L., Loane, M., Wellesley, D., Addor, M. C., Arriola, L., Bakker, M. K., . . . Garne, E. (2014). Prenatal diagnosis and epidemiology of multicystic kidney dysplasia in Europe. *Prenatal Diagnosis, 34*(11), 1093–1098. doi:10.1002/pd.4433

Winyard, P. J., Bharucha, T., De Bruyn, R., Dillon, M. J., van't Hoff, W., Trompeter, R. S., . . . Rees, L. (2006). Perinatal renal venous thrombosis: Presenting renal length predicts outcome. *Archives of Disease in Childhood—Fetal Neonatal Edition, 91*(4), F273–F278. doi:10.1136/adc.2005.083717

Woodard, J. R. (1978). The prune belly syndrome. *Urologic Clinics of North America, 5*(1), 75–93. doi:10.1111/j.1464-410X.1978.tb03646.x

World Health Organization. (n.d.). Male circumcision for HIV prevention. Retrieved from https://www.who.int/hiv/topics/malecircumcision/en

Yang, Y., Hou, Y., Niu, Z. B., & Wang, C. L. (2010). Long-term follow-up and management of prenatally detected, isolated hydronephrosis. *Journal of Pediatric Surgery, 45*(8), 1701–1706. doi:10.1016/j.jpedsurg.2010.03.030

Yohannes, P., & Hanna, M. (2002). Current trends in the management of posterior urethral valves in the pediatric population. *Urology, 60*(6), 947–953. doi:10.1016/S0090-4295(02)01621-7

Youn, J. K., Kim, H.-Y., Huh, Y.-J., Han, J.-W., Kim, S.-H., Oh, C., . . . Jung, S.-E. (2018). Inguinal hernia in preterms in neonatal intensive care units: Optimal timing of herniorrhaphy and necessity of contralateral exploration in unilateral presentation. *Journal of Pediatric Surgery, 53*(11), 2155–2159. doi:10.1016/j.jpedsurg.2018.02.056

Zaritsky, J. J., & Warady, B. A. (2014). Chronic kidney disease in the neonate. *Clinics in Perinatology, 41*(3), 503–515. doi:10.1016/j.clp.2014.05.002

CHAPTER 19

Fluids, Electrolytes, and Acid–Base Balance

Shreyas Arya and Vivek Narendran

INTRODUCTION

The maintenance of fluid, electrolytes, and acid–base balance are vital components of neonatal care. This is particularly true for very low birth weight (VLBW) infants, as they require parenteral fluids for prolonged periods and have unique limitations related to their immature kidneys and skin. Rapid maturational changes in various organs and fluid shifts that occur after birth confound the issue further. Critically ill newborns are at additional risk for morbidity and mortality due to fluid and electrolyte imbalance.

WATER

Physiology. Water is the main component of the human body. It is distributed both inside and outside the cells. Thus, the total body water (TBW) is a sum of intracellular water (ICW) and extracellular water (ECW). ICW is the total amount of water in all the body's cells. ECW is the total amount of water outside the cells, which includes the water in the interstitial space and in the intravascular space (plasma).

The distribution of TBW between intracellular and extracellular spaces depends on the relative concentration of solutes (relative osmolality). The total number of solute particles in solution determines the osmolality of a solution. Osmolality values are expressed in osmoles or milliosmoles per kilogram of water (Osm/kg or mOsm/kg). Cell membranes are completely permeable to water but not to most solutes; hence, water shifts from one compartment to the other until equilibrium is established between the osmolalities on both sides of the membrane. The osmolality of intracellular and extracellular spaces, therefore, is equal, although the composition of ICW is vastly different from that of ECW; for example, sodium (Na^+) is the major extracellular cation, whereas potassium (K^+) is the main intracellular cation. In each compartment, the main solute acts to keep water within the compartment:

- The volume of the intracellular compartment is maintained mainly by potassium salts and is regulated by the Na^+/K^+ cellular pump.
- The volume of the extracellular compartment is maintained mainly by sodium salts and is regulated by the kidneys.
- The volume of the intravascular compartment is maintained mainly by the colloidal osmotic pressure of plasma proteins and is regulated by the endocrine system and the kidneys.

Changes in Water Distribution. In the first trimester of gestation, TBW constitutes more than 90% of the body weight; however, its relative contribution to body weight declines as the fetus matures. TBW decreases to 80% at 32 weeks' gestation, 78% at 40 weeks' gestation, and approximately 60% to 65% at the end of the first year of life. The ratio of ECW to ICW also changes with growth. ECW declines from approximately 60% of body weight in the second trimester to about 45% at term. Correspondingly, ICW increases from about 25% of body weight in the second trimester to approximately 33% at term. Thus, the decrease in TBW as the infant matures is attributed largely to the decrease in ECW compartment (Figure 19.1).

Superimposed on the gradual contraction of ECW that occurs as the fetus approaches term is an acute expansion of ECW that occurs at birth. This is due to (a) placental transfusion, (b) reabsorption of lung fluid, and (c) shift of water and electrolytes from the intracellular to the extracellular space (Baumgart & Costarino, 2000). The newborn at birth is, therefore, in a state of excess extracellular fluid, a condition that is particularly prominent in preterm infants (TBW and ECW are greater at lower gestational ages). After the first 24 to 48 hours of life, the infant undergoes a diuresis phase. This results in the loss of excess ECW and is termed as physiologic weight loss (5%–10% in term infants and up to 15% in very preterm infants). Any disruptions in this normal transition can lead to imbalances in fluid and electrolyte homeostasis, leading to morbidity. For example, in preterm infants, iatrogenic administration of large amounts of fluids can potentially increase the risk of a symptomatic patent ductus arteriosus (PDA; Bell, Warburton, Stonestreet, & Oh, 1980), necrotizing enterocolitis (NEC; Bell, Warburton, Stonestreet, & Oh, 1979), and bronchopulmonary dysplasia (BPD; Van Marter, Leviton, Allred, Pagano, & Kuban, 1990).

Water Balance and Requirements. Water balance in neonates is under the direct control of antidiuretic hormone (ADH), which is also known as vasopressin. ADH is secreted by the hypothalamus when the serum osmolality is greater than 285 mOsm/kg or there is intravascular volume depletion. It regulates intravascular volume by changing water permeability of the collecting ducts in the kidneys. A mature adult kidney can concentrate urine

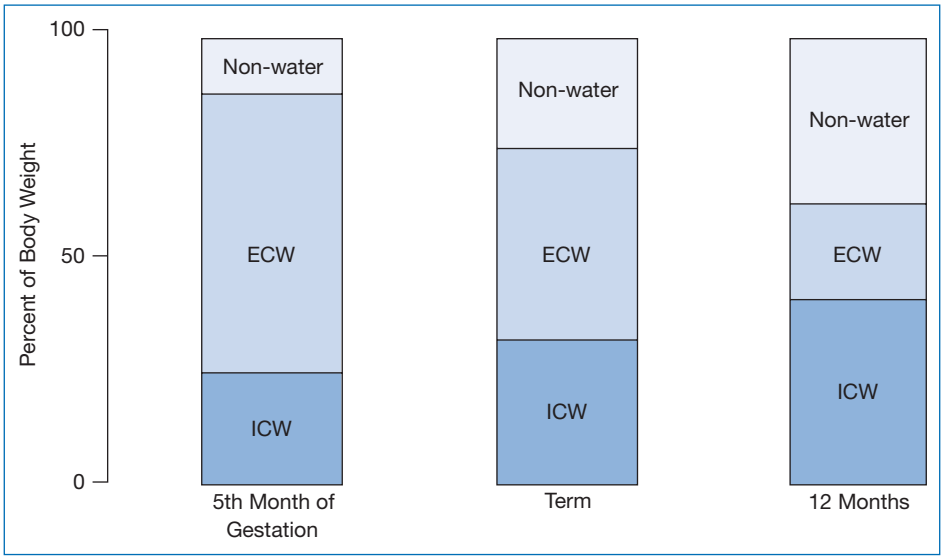

FIGURE 19.1 Changes in body water distribution. Note the relative decrease in ECW compartment.
ECW, extracellular water; ICW, intracellular water.

up to a maximum of 1,500 mOsm/kg or dilute to a minimum of 50 mOsm/kg based on the body's fluid status. However, this concentrating ability is remarkably diminished in neonates. A term neonate can maximally concentrate urine up to 800 mOsm/kg and a preterm neonate to only 600 mOsm/kg. This inability to sufficiently concentrate urine, proportionate to the demands of the body, predisposes neonates to a significant risk for water and electrolyte imbalances.

Maintaining optimal water and electrolyte composition depends on anticipating water losses and replacement with pertinent maintenance fluids. Table 19.1 highlights factors that impact water loss in neonates. Maintenance fluids are defined as the amount of water and electrolytes required to maintain a patient in a neutral water balance. These include replacement of urine, gastrointestinal losses, and insensible water loss (IWL). Preterm infants are particularly susceptible to water imbalances due to immature renal function, very high IWL through the skin and respiratory tract, higher body surface area to body mass ratio, and acuity of illness (Baumgart & Costarino, 2000). Table 19.2 provides approximate requirements for the maintenance fluids (mL/kg/day) for infants up to a week of life. However, further titrations are made by assessing the clinical status of the patient and accounting for factors that might increase or decrease fluid loss. For example, phototherapy increases IWL, whereas the use of double-walled and humidified incubators reduces IWL. However, the use of newer devices for phototherapy combined with modern incubators has significantly decreased their effects on IWL (Maisels & McDonagh, 2008).

Postnatal Adaptations. Most preterm infants follow a distinctive postnatal pattern of diuresis consisting of three phases: (a) the prediuretic phase, (b) the diuretic phase, and (c) the homeostatic phase (Lorenz, Kleinman, Ahmed, & Markarian, 1995). The *prediuretic phase* occurs in the first 24 to 48 hours of life wherein the glomerular filtration rate (GFR), urinary output (UOP), and sodium and potassium excretion are all very low. Water is lost mainly by IWL. The total fluid requirement is calculated to account mainly for the IWL (Tables 19.1 and 19.2) and supplementation with sodium, chloride, or potassium is not done. As very preterm infants have significant skin (transepidermal) water losses, they are predisposed to hemoconcentration and hypernatremia even in the prediuretic phase.

TABLE 19.1
FACTORS AFFECTING WATER LOSS IN NEONATES

Increasing Water Loss	Decreasing Water Loss
Water Loss From the Skin	
Low gestational age	High humidity in incubator
Radiant warmer	Double-walled incubator
Hyperthermia	Plastic heat shield
Skin breakdown	
Phototherapy	
Congenital defects (e.g., gastroschisis)	
Water Loss From the Respiratory Tract	
Tachypnea	Use of humidified gas
Inadequate humidification	
Renal Water Loss	
Diuretic agents (e.g., furosemide)	Renal failure
Osmotic diuresis (hyperglycemia, mannitol)	Inappropriate secretion of antidiuretic hormone
Congenital adrenal hyperplasia	Congestive heart failure

The *diuretic phase* usually begins on day 2 to 5 of life when the UOP, sodium, and potassium excretion increases abruptly. This phase seems to be triggered by the atrial natriuretic peptide (ANP),

TABLE 19.2

APPROXIMATE MAINTENANCE REQUIREMENTS OF NEWBORNS IN THE FIRST WEEK OF LIFE

	Birth Weight			
Time Period	**<750 g**	**750–1,000 g**	**1,001–1,500 g**	**>1,500 g**
First 48 hours	100–200	80–150	60–100	60–80
Day 3–7	120–200	100–150	80–150	100–150

Note: Amounts are given as mL/kg/day.

TABLE 19.3

ELECTROLYTE CONTENT OF BODY FLUIDS

Fluid	Sodium (mmol/L)	Potassium (mmol/L)	Chloride (mmol/L)
Stomach	20–80	5–20	100–150
Small intestine	100–140	5–15	90–120
Bile	120–140	5–15	90–120
Ileostomy	45–135	3–15	20–120
Diarrheal stool	10–90	10–80	10–110

Source: With permission from Martin, R. J., Fanaroff, A. A., & Walsh, M. C. (Eds.). (2015). *Fanaroff and Martin's neonatal-perinatal medicine: Diseases of the fetus and infant* (10th ed.). Philadelphia, PA: Saunders.

which is released by myocardial cells in response to atrial stretching or filling. This occurs due to the physiologic decrease in pulmonary vascular resistance after birth that leads to increased venous return to the left atrium and the release of ANP. This ANP in turn causes increased natriuresis (Modi, 2003). In this phase, water intake is adjusted to maintain a normal serum sodium concentration and to maintain total weight loss below 10% in term and below 15% in preterm infants. Sodium and potassium supplementation is also started.

In the *homeostatic phase*, which follows the diuretic phase, UOP stabilizes. The goal of fluid and electrolyte intake in this phase is to maintain water and electrolyte balance and to provide nutrition for adequate growth. Infants normally grow at a rate of 10 to 20 g/kg/day. Because three quarters of this new body mass is fluid, the total fluids given to an infant should provide a net positive balance of 10 to 15 mL/kg/day.

Pathologic Fluid and Electrolyte Losses. Certain clinical conditions predispose infants to pathologic fluid and electrolyte loss. Commonly encountered situations in the neonatal intensive care unit (NICU) include loss of gastric fluid due to Replogle tube placement or vomiting, loss of enteric fluids due to an ostomy, and fluid and electrolyte losses in stools. Table 19.3 highlights the electrolyte concentration of different body fluids and can be used to estimate the specific losses and for calculating adequate replacement.

ELECTROLYTES

Sodium. Sodium is the main extracellular cation accounting for more than 90% of the solutes in the extracellular space. It is absorbed in both the small intestine and the colon, the largest amount being absorbed in the jejunum. Sodium absorption involves several mechanisms:

- Passive absorption along with glucose, secondary to the flow of water
- Active absorption, uncoupled with glucose, involving the Na^+/K^+ pump
- Active absorption in exchange for hydrogen ions (H^+)

The overall process is very efficient. The kidneys excrete sodium, which is first filtered by the glomeruli and later reabsorbed throughout the tubules and the collecting ducts. Most of the sodium is absorbed with chloride (Cl^-), with lesser amounts absorbed in exchange with K^+ or H^+. Under normal circumstances, 96% to 99% of filtered sodium is reabsorbed. The main factors regulating sodium resorption are the oncotic and hydrostatic pressures in the peritubular capillaries of the kidneys. The mineralocorticoid aldosterone is also critical in maintaining sodium levels. When there is volume depletion, aldosterone is secreted by the renin–angiotensin–aldosterone system in the juxtaglomerular cells of the kidney. Under the influence of this steroid hormone, there is sodium and water absorption in exchange for K^+ and H^+. Although ADH does not affect the excretion of sodium directly, it can influence the serum sodium concentration indirectly as it regulates the excretion and resorption of free water.

Emergency Alert: Both hypernatremia and hyponatremia in preterm infants have been associated with adverse neurologic outcomes at 2 years of age. Additionally, the risk appears to be directly proportional to the magnitude of the variation in serum sodium levels during the NICU stay (Baraton et al., 2009).

The sodium concentration in human milk is 12 to 20 mEq/L. The recommendation for growing preterm infants is 3 to 5 mEq/kg/day (Tsang, Lucas, Uauy, & Zlotkin, 2005). Because of their high urinary loss of sodium, VLBW infants (those weighing <1,500 g) may temporarily require up to 8 mEq/kg/day by the end of the first week of life. Thereafter, urinary losses in these infants decrease. The normal serum sodium concentration ranges from 130 to 150 mEq/L.

Disorders of sodium balance are listed in Box 19.1.

Hyponatremia. Hyponatremia is defined as a serum sodium level below 130 mEq/L. There are three major mechanisms for this:

- Increased sodium loss
- Inadequate sodium intake
- Inability to excrete excess water (dilution effect)

Box 19.1

DISORDERS OF SODIUM BALANCE

Hyponatremia

- VLBW infant-fed unfortified human milk or standard term formula
- Perinatal asphyxia
- Renal failure, congestive heart failure
- SIADH (RDS, IVH, pneumothorax)
- Diuretics
- Sodium losses through the gut
- Hypotonic fluid administered to mother during labor
- Adrenal insufficiency (congenital adrenal hyperplasia)

Hypernatremia

- Dehydration (vomiting, diarrhea, IWL through immature skin)
- Diabetes insipidus (central and nephrogenic)
- Osmotic diuresis (hyperglycemia, mannitol)
- Overhydration (excessive administration of sodium-containing fluids)
- Medication errors

IVH, intraventricular hemorrhage; IWL, insensible water loss; RDS, respiratory distress syndrome; SIADH, syndrome of inappropriate secretion of antidiuretic hormone; VLBW, very low birth weight.

It is therefore important to first delineate the etiology of hyponatremia and assess volume status prior to instituting therapy. For example, an infant with hyponatremia due to inability to excrete water because of acute kidney injury requires fluid restriction, while an infant with excessive urinary or stool water and sodium losses requires fluid replacement.

Increased Sodium Loss and Inadequate Intake. This is most commonly seen after the first week of life in growing VLBW infants, fed either human milk or standard term formulas. These infants can have a negative sodium balance in the first weeks of life because of an inadequate sodium intake and transient unresponsiveness of the renal tubules to aldosterone (Baumgart & Costarino, 2000). VLBW infants may require up to 8 mEq/kg/day or higher to maintain a positive sodium balance. Usually, the lower the gestational age, the higher the sodium intake needed.

Abnormalities in either the production of aldosterone (congenital adrenal hyperplasia) or the renal responsiveness to aldosterone (pseudohypoaldosteronism) can also lead to increased sodium losses and hyponatremia. Variable degrees of hyperkalemia and metabolic acidosis are associated with the previously noted disorders due to the influence of aldosterone on K^+ and H^+ excretion.

Extrarenal losses of sodium occur with vomiting and diarrhea. Loop diuretics like furosemide are notorious for causing hyponatremia.

Inability to Excrete Excess Water. In neonates, hyponatremia due to retention of water (dilution) occurs after an acute kidney injury leading to decreased GFR. This is seen after perinatal asphyxia or following nephrotoxic drug therapy. Another mechanism at play during perinatal asphyxia is the increased secretion of ADH (syndrome of inappropriate secretion of antidiuretic hormone, or SIADH). Severe respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), and pneumothorax can also predispose newborns to hyponatremia due to SIADH.

Hyponatremia can also be iatrogenic secondary to excessive administration of hypotonic fluids to the mother during labor, feeding diluted formula, or following resuscitation with hypotonic fluids. Whenever the serum sodium concentration decreases, serum osmolality declines, causing water to move into cells. This phenomenon also occurs in the brain cells, causing signs and symptoms characteristic of hyponatremia. Vomiting, lethargy, and apnea may occur with various degrees of hyponatremia. Seizures and coma are not seen unless the serum sodium concentration falls below 115 mEq/L.

Treatment is directed both at the underlying disorder and volume replacement with sodium chloride (NaCl)–containing solutions. The amount of sodium needed is calculated using this standard formula:

$$\begin{aligned}&\text{Total sodium required (mEq)}\\&\quad = 0.6 \times \text{Weight (kg)}\\&\qquad \times (\text{Desired serum } Na^+ - \text{Observed serum } Na^+)\end{aligned}$$

Quality and Safety: This correction is done slowly over several hours. The rate of correction should not exceed 10 to 12 mEq/L/day (or 0.5 mEq/L/hour). The target is a serum sodium concentration of about 135 mEq/L. Rapid correction of hyponatremia puts the infant at risk for a condition known as central pontine myelinolysis.

This general rule has two exceptions:

- In presence of overt or impending shock, normal saline should be given intravenously and rapidly at 10 to 20 mL/kg over 20 to 30 minutes; treatment is repeated until arterial blood pressure is normal.
- If hyponatremic seizures are diagnosed, hypertonic saline (3%) should be infused. These seizures usually abate with correction in serum sodium concentration of 3 to 5 mEq/L. Care must be taken to avoid overcorrection.

Hypernatremia. Hypernatremia is defined as a serum sodium level over 150 mEq/L. It is also caused by three major mechanisms:

- Increased loss of free water (renal or extrarenal)
- Decreased water replacement
- Excess sodium intake

Whenever hypernatremia occurs, the serum osmolality increases, leading to water moving out of the cells into the extracellular space to achieve an osmotic equilibrium between intracellular and extracellular fluid. This attempt to equilibrate results in volume depletion of the intracellular space. To counteract this phenomenon, brain cells (neurons) have the unique ability to generate new solutes called idiogenic osmoles. These are substances (amino acids, polyols, trimethylamines) synthesized by the brain cells as a protective response to serum hyperosmolality. Idiogenic osmoles are produced and catabolized slowly and hence are effective only if hyperosmolality does not develop too rapidly. For this reason, correction of hypernatremia with hypotonic solutions should not be performed rapidly as cerebral edema can occur due to movement of water into brain cells.

Increased Loss of Free Water and Decreased Replacement. This is referred to as hypernatremia with dehydration. Water loss in a neonate can occur through the immature skin, kidneys, or the gastrointestinal tract. Hypernatremia due to excess IWL through the immature skin is particularly pronounced in VLBW infants. The magnitude of these losses is inversely related to gestational age. In these infants, weight, UOP, serum sodium level, and glucose concentrations should be monitored closely. Adequate fluid replacement and sodium restriction during the first 3 to 5 days of life may prevent hypernatremia. IWL is minimized with the use of double-walled incubators with a high relative humidity.

Excessive renal water loss occurs when an increased amount of solute such as glucose needs to be excreted (osmotic diuresis) or secondary to diabetes insipidus (DI). DI is caused by either decreased production of ADH by the hypothalamus (central DI) or by renal unresponsiveness to ADH (nephrogenic DI). In both these conditions, the infant presents with hypernatremia, polyuria, decreased feeding, and poor growth. These infants frequently require periodic fluid replacements to compensate for ongoing renal losses. Water loss similarly may occur from the gastrointestinal tract following vomiting, diarrhea, or increased ostomy output.

Quality and Safety: Hypernatremia with dehydration must be corrected slowly to avoid cerebral edema. Intravascular volume should be restored relatively quickly with isotonic fluids, but water deficits should be corrected slowly with administration of hypotonic fluids. As a general rule, serum sodium should not decrease by more than 0.5 mEq/kg/hour (or 10–12 mEq/kg/day).

Excessive Sodium Administration. This is referred to as hypernatremia with overhydration. Excessive sodium administration can be caused inadvertently by administration of certain medications like gentamicin, heparin, calcium gluconate, sodium bicarbonate, sodium chloride flushes, and fluids to keep central lines patent (Bhatia, 2006). VLBW infants are particularly at risk from these "large" sodium loads. Treatment of this iatrogenic form of hypernatremia involves sodium restriction.

Potassium. Potassium is the main intracellular cation. Its concentration in cells is maintained by the membrane Na^+/K^+ pump, and it is involved in the regulation of cell membrane potential. Small variations in serum potassium concentration have significant effects, particularly on the myocardial cells.

Dietary potassium is mainly absorbed in the small intestine by passive absorption, and is actively secreted in the colon. The kidneys excrete potassium, and most filtered potassium is reabsorbed in the proximal tubule. Potassium is then secreted by the distal tubules in exchange for sodium in a process regulated by aldosterone. Hence, preterm infants with BPD that require chronic diuretic therapy (most diuretics are natriuretic) often need replacement with oral potassium chloride (KCl) to correct their electrolyte imbalance. The potassium requirement for both preterm and full-term infants is 2 to 3 mEq/kg/day. The normal serum concentration is 3.5 to 5 mEq/L.

Disorders of potassium balance are listed in Box 19.2.

Box 19.2

DISORDERS OF POTASSIUM BALANCE

Hypokalemia

- Renal losses: chronic diuretics, renal tubular acidosis, Bartter's syndrome
- Inadequate potassium intake
- Gastrointestinal losses: vomiting, diarrhea, nasogastric aspiration, ostomy output

Hyperkalemia

- Hemolyzed blood sample
- Excessive intake
- Impaired excretion: renal failure, congenital adrenal hyperplasia, pseudohypoaldosteronism
- Potassium-sparing diuretics
- Metabolic acidosis

Hypokalemia. Hypokalemia is defined as a serum potassium level below 3.5 mEq/L. It can be caused by increased renal losses (diuretics, renal tubular acidosis [RTA], and Bartter's syndrome), increased gastrointestinal losses (diarrhea, vomiting, continuous nasogastric aspiration, and ostomy output), or inadequate intake. The use of potassium-sparing diuretics may decrease the incidence of hypokalemia in the NICU.

Hypokalemia manifests through its effects on muscle cells. Although abdominal distention, diminished bowel motility, weakness, and lethargy are described, the cardiac effects are of much greater concern. An electrocardiogram (EKG) is a better measure of serious toxicity than the serum potassium concentration. **Emergency Alert: EKG changes associated with hypokalemia include a depressed ST segment, a flattened T wave, and a prominent U wave. A prolonged P-R interval, widening QRS complex, and various arrhythmias may follow, if untreated.**

Treatment involves potassium replacement. KCl should be given very slowly (<0.3 mEq/kg/hour) with frequent serum and EKG monitoring. Rapid intravenous (IV) administration of potassium may in itself cause fatal arrhythmias.

Hyperkalemia. Hyperkalemia is defined as a serum potassium level over 6.5 mEq/L. It can be caused by an excessive intake of potassium, impaired excretion (renal failure, congenital adrenal hyperplasia, and pseudohypoaldosteronism), or with severe metabolic acidosis (increased movement of potassium from the intracellular to the extracellular space). Factitious hyperkalemia may be associated with hemolysis (breakdown of red blood cells) and must be ruled out. Hyperkalemia occurs in approximately 50% of infants whose birth weight is less than 1,000 g, and is thought to occur due to decreased activity of the Na^+/K^+ pump. Thus, potassium should not be added to IV fluids in the first few days of life until good UOP is established. Cardiac toxicity is a serious complication of hyperkalemia and is better reflected by EKG changes than by the serum concentration. The typical EKG sequence is peaked or "tented" T waves, disappearance of P waves, and a widening QRS complex, which fuses with the T wave to form a sine wave. Ventricular fibrillation and cardiac arrest may follow if the serum potassium level remains untreated.

Treatment is directed at the underlying disorder. All potassium-containing fluids and supplements should be stopped immediately. Management of hyperkalemia with EKG changes includes the following:

- 10% calcium gluconate (100–200 mg/kg/dose, IV) is given to counteract the effects of hyperkalemia on the myocardium cells (*stabilizing the myocardial membrane against arrhythmias*). It does not decrease the serum potassium concentration.
- Sodium bicarbonate (1–2 mEq/kg, IV) is given to raise the blood pH and consequently increase potassium influx into cells.
- Nebulized beta-agonist agent (albuterol) is administered to increase intracellular uptake of potassium.
- Infusion of glucose and insulin is done, at a ratio of 4 g of glucose to 1 U of insulin, to increase intracellular uptake of potassium.
- Loop diuretics (furosemide; 1 mg/kg, IV) are given to increase renal excretion of potassium.
- Potassium-binding resin, Kayexalate (1 g/kg, by rectum or by mouth), is given to increase intestinal excretion.

Most of these measures are transient, as they do not decrease total body potassium but just move it intracellularly. Hence, if the serum potassium continues to rise and exceeds 8 mEq/L, peritoneal dialysis or exchange blood transfusions, using a mixture of washed red blood cells and fresh frozen plasma, may be necessary.

Chloride. Chloride is the main inorganic anion in the extracellular fluid, and together with sodium is responsible for maintaining plasma volume. Chloride is typically administered with Na^+ or K^+

Box 19.3

DISORDERS OF CHLORIDE BALANCE

Hypochloremia

- Decreased intake: older soy-based formulas
- Increased gastrointestinal losses: vomiting (pyloric stenosis), continuous gastric aspiration
- Congenital chloride diarrhea
- Increased renal losses: diuretics, Bartter's syndrome

Hyperchloremia

- Increased bicarbonate losses: renal tubular acidosis
- Excessive administration (with NaCl: absolute or relative)
- Hypertonic dehydration (apparent hyperchloremia)

as either NaCl or KCl in diet or in intravenous fluids. Intestinal absorption is passive in the jejunum and occurs secondary to sodium absorption. In the ileum and colon, chloride is actively absorbed in exchange for bicarbonate (HCO_3^-). Normally, only minimal amounts of chloride are lost in the feces. Similar to sodium, it is filtered by the glomeruli and reabsorbed throughout the tubules and collecting ducts. Normally, 99% of the filtered chloride is reabsorbed.

Chloride resorption is inversely related to bicarbonate resorption; hence, their serum concentrations are also inversely correlated, which keeps the total anion concentration (Cl^- and HCO_3^-) constant and maintains electrical neutrality. For this reason, although chloride has no buffer effect, it plays an important part in the acid–base regulation. When chloride is retained in the body, the serum bicarbonate level declines and metabolic acidosis follows. When chloride is lost from the body, the serum bicarbonate level rises and metabolic alkalosis ensues.

The recommended oral intake for preterm infants is 105 to 177 mg/kg/day (Agostoni et al., 2010). Normal serum chloride concentrations are 90 to 112 mEq/L in full-term infants and 100 to 115 mEq/L in preterm infants.

Disorders of chloride balance are listed in Box 19.3.

Hypochloremia. Hypochloremia is defined as a serum chloride level below 90 mEq/L and is caused by either a diminished intake or increased loss of chloride (gastrointestinal or renal). Clinical manifestations include metabolic alkalosis, hypokalemia, and, when chronic, failure to thrive.

Insufficient intake has been reported with soy formulas due to their low chloride content. The diagnosis of insufficient intake is based on the dietary history and the absence of urinary chloride, which indicates a normal ability to retain chloride to compensate for the low intake. Chloride losses independent of sodium and potassium may occur from prolonged vomiting in the form of hydrochloric acid (HCl) in pyloric stenosis or continuous aspiration of gastric contents via nasogastric tubes (e.g., in NEC).

Congenital chloride diarrhea is a rare disorder of severe diarrhea, beginning at birth, caused by impairment of the active Cl^-/HCO_3^- transport system in the ileum and colon. It is caused by a mutation in the *SLC26A3* gene responsible for encoding the exchange transporter in the intestine. However, these infants usually have normal electrolyte absorption in the jejunum. Analysis of stools shows an acidic pH and a greatly increased chloride concentration (>90 mmol/L; Elrefae, Elhassanien, & Alghiaty, 2013). Diarrhea is caused by the osmotic effect of excess chloride, which then leads to metabolic alkalosis and hypokalemia. The urine chloride is also decreased. Treatment involves lifelong supplementation and replacement of appropriate electrolytes. Other treatments include proton pump inhibitors and oral butyrate.

The most common cause of increased renal loss of chloride is diuretic therapy. **Quality and Safety: Chronic administration of furosemide, used often in the management of BPD, may cause chloride deficiency with secondary metabolic alkalosis.** Alkalosis, in turn, causes compensatory hypoventilation and an increase in the partial pressure of carbon dioxide (P_{CO_2}) in blood. This clinical picture can simulate pulmonary edema; however, the treatment should not be additional diuretic therapy but rather correction of the underlying hypochloremia.

Metabolic alkalosis with hypochloremia, hypokalemia, and hypercalciuria due to increased renal loss of chloride is the characteristic feature of Bartter's syndrome. These infants also have failure to thrive and episodes of dehydration. It is caused by a mutation in the Na^+-K^+-Cl^- cotransporter and is inherited in an autosomal recessive pattern. Elevated prostaglandin E concentrations are observed in the urine. Replacement with NaCl and KCl, maintenance of intravascular volume, and indomethacin (a prostaglandin antagonist) are the mainstays of treatment (Rodriguez-Soriano, 1998).

Hyperchloremia. Hyperchloremia is defined as a serum chloride level over 115 mEq/L. It is caused by either bicarbonate depletion or by excessive chloride intake and is commonly associated with metabolic acidosis. Diarrhea is the most common cause of hyperchloremic metabolic acidosis, as chloride is absorbed with sodium, and bicarbonate is excreted with potassium in the intestine.

Emergency Alert: Increased loss of bicarbonate occurs with RTA (type II or proximal type). In this condition, the renal threshold for bicarbonate drops and absorption of bicarbonate does not occur until the serum levels drop approximately below 15 mEq/L. The result is a hyperchloremic metabolic acidosis. The condition is often self-limited, as the proximal tubular length increases and function matures. The diagnosis is based on demonstrating a renal bicarbonate reabsorption threshold that is lower than normal.

Hyperchloremia may follow excessive administration of NaCl. Overtreatment with NaCl may be absolute, as in accidental errors in administration, or relative, as in renal failure where the excretion is impaired. Finally, apparent hyperchloremia, together with increased serum concentrations of other electrolytes, can occur with dehydration when there is a water deficit in relation to solute.

Calcium and Phosphorus. Calcium (Ca) is the most abundant mineral in the human body and is an essential component of the skeleton. It plays an important role in muscle contraction, neural transmission, and blood coagulation. Phosphorus (P) is equally essential for bone mineralization. About 80% of phosphorus is present in the bones and the remaining 20% is incorporated into energy storage molecules as adenosine triphosphate (ATP), which is essential for cell metabolism.

In the third trimester, the placental accretion of calcium is about 100 to 130 mg/kg/day and that of phosphorus is 60 to 70 mg/kg/day. In preterm babies, unfortified human milk fails to provide comparable levels of mineral retention, predisposing these infants to relative osteopenia known as metabolic bone disease of prematurity (Abrams, 2013).

Recommendations for enteral intake in preterm infants are 120 to 140 mg/kg/day of calcium and 60 to 90 mg/kg/day of phosphorus (Agostoni et al., 2010). With parenteral nutrition, a calcium intake of 60 to 80 mg/kg/day and a phosphorus intake of 45 to 60 mg/kg/day is recommended (Tsang et al., 2005). **Quality and Safety: To avoid precipitation in the parenteral solution,**

the calcium concentration should be maintained between 500 and 600 mg/L (12.5–15 mmol/L), and the phosphorus concentration should be maintained between 390 and 470 mg/L (12.5–15 mmol/L).

Calcium. Calcium transport in the intestine occurs by both passive and active processes. Active intestinal transport involves carriers called calcium-binding proteins. Vitamin D in its active form, 1, 25-dihydroxyvitamin D or calcitriol, is essential for the active process. Parathyroid hormone (PTH) is involved in the production of 1,25-dihydroxyvitamin D. Vitamin D deficiency and intestinal malabsorption due to any cause can impair calcium transport. **Quality and Safety: Corticosteroids diminish calcium absorption by inhibiting its transfer in the intestinal mucosa. Similarly, anticonvulsants can inhibit intestinal transfer of calcium (phenytoin) and interfere with vitamin D metabolism (phenobarbital and phenytoin).**

Calcium is present in the serum in three forms: ionized (50%), bound to proteins—mainly albumin (40%), and complexed with organic and inorganic compounds (10%). The ionized calcium is the only biologically active form. The calcium bound to albumin serves as a reserve. Therefore, measuring the ionized calcium level is more clinically relevant than the total serum calcium concentration. The affinity of calcium to albumin is increased by metabolic alkalosis and decreased by acidosis. In addition, with every 1 g/dL decrease in serum albumin, the total serum calcium decreases by 0.8 mg/dL but the ionized calcium remains unchanged. The serum calcium concentration is maintained within narrow limits by the action of PTH, 1,25-dihydroxyvitamin D, and calcitonin. PTH and 1,25-dihydroxyvitamin D increase the serum calcium level, while calcitonin reduces it. PTH secretion is driven by the serum ionized calcium concentration via the calcium-sensing receptors in the parathyroid cells.

The kidneys excrete calcium and filtered calcium is reabsorbed in most segments of the renal tubules. PTH increases tubular resorption of calcium, whereas calcitonin increases calcium excretion.

Disorders of calcium balance are listed in Box 19.4.

Box 19.4

DISORDERS OF CALCIUM BALANCE

Hypocalcemia

- *Early*
  - Preterm infant
  - Infant of diabetic mother
  - Perinatal asphyxia
  - Maternal anticonvulsant therapy
- *Late*
  - Hyperphosphatemia (increased dietary intake, renal failure)
  - Cow milk–based feeding
  - Hypomagnesemia
  - Hypoparathyroidism
  - Vitamin D deficiency

Hypercalcemia

- Excessive administration of calcium or vitamin D (or both)
- Hypophosphatasia
- Subcutaneous fat necrosis
- Williams' syndrome
- Idiopathic hypercalcemia
- Hyperparathyroidism
- Bartter's syndrome
- Familial hypocalciuric hypercalcemia

Hypocalcemia. Neonatal hypocalcemia is defined as an ionized serum calcium concentration below 4.4 mg/dL (1.1 mmol/L) in full-term infants. For preterm infants, insufficient normative data at different gestational ages exists; hence, a total serum calcium concentration below 7 mg/dL (1.75 mmol/L) remains a practical definition. Hypocalcemia conventionally is divided into early hypocalcemia, which occurs in the first 2 to 4 days of life, and late hypocalcemia, which occurs after the first 4 days, usually at about 1 week of age.

There is a physiologic fall in the calcium concentration during the first 48 hours of life. This is due to the abrupt interruption of maternal calcium supply and low dietary intake. In preterm infants, this fall in calcium is more rapid and inversely proportional to gestational age. Factors that contribute to early hypocalcemia in preterm neonates include inadequate PTH release, decreased responsiveness of renal tubules to PTH, and relative resistance to 1,25-dihydroxyvitamin D.

Infants of diabetic mothers are at increased risk of hypocalcemia due to hypomagnesemia. Mothers with diabetes have increased losses of magnesium in the urine, which in turn causes fetal hypomagnesemia and secondary hypoparathyroidism. Improvement in diabetes control during pregnancy has been associated with lower occurrence of hypocalcemia (Banerjee et al., 2003).

Hypocalcemia in the first few days of life is also seen following birth asphyxia. These infants have increased serum calcitonin and a relative increase in phosphorus load due to reduced glomerular filtration. Treatment of associated acidosis with bicarbonate may further aggravate hypocalcemia in these infants, due to increased calcium binding to albumin as mentioned earlier.

Late hypocalcemia typically occurs by the end of the first week of life. It is seen more often in term than in preterm infants and is caused by the relative resistance of renal tubules to PTH. This leads to increased phosphate retention and hypocalcemia. Low serum magnesium levels lead to hypocalcemia due to their inhibitory effect on PTH secretion (see the section on Magnesium later in the chapter). Infants fed cow's milk are also more prone to late hypocalcemia due to its high phosphorus content. Maternal vitamin D deficiency may be a predisposing factor; hence, vitamin D supplementation (400 IU) for all infants and 600 IU for breastfeeding and pregnant mothers is currently recommended. **Quality and Safety: Furosemide therapy can cause hypocalcemia and nephrolithiasis secondary to calciuresis.** Phototherapy also appears to be a cofactor associated with neonatal hypocalcemia, particularly in preterm infants. The mechanism is incompletely understood.

Neonatal hypoparathyroidism is characterized by low PTH, hypocalcemia, and hyperphosphatemia. It can be caused by structural abnormalities of the parathyroid glands, defects in the PTH molecule, or dysregulation of PTH secretion. In rare cases, late hypocalcemia can occur as a consequence of subclinical maternal hyperparathyroidism: maternal hypercalcemia leads to fetal hypercalcemia, which suppresses the fetal parathyroid glands. After birth, when the maternal source of calcium is no longer available, the suppressed parathyroid glands are unable to maintain a normal serum calcium concentration. Because maternal

hyperparathyroidism is often asymptomatic, neonatal hypocalcemia may provide the initial clue to maternal disease.

Neonatal hypocalcemia may be asymptomatic or can cause symptoms such as irritability, tremors, poor feeding, muscle twitching, and seizures. Diagnosis of hypocalcemia is based on definitions outlined earlier. Serum magnesium level should also be measured due to its effects on calcium homeostasis.

Several factors complicate the choice of treatment for neonatal hypocalcemia: (a) In most cases, the condition is asymptomatic and self-limited; (b) It may be associated with seizures without being the cause of seizures; (c) It may coexist with other perinatal complications, such as asphyxia and hypoglycemia, which can cause similar clinical signs. If the hypocalcemia is asymptomatic, 10% calcium gluconate (9.4 mg of elemental calcium per mL) may be given orally at a rate of 75 mg/kg/day divided into six equal doses. If hypocalcemia is symptomatic (e.g., seizures), 10% calcium gluconate must be given intravenously at a rate of 2 mL/kg over 10 minutes while the heart rate is being continuously monitored and the infusion stopped at the first sign of bradycardia. For late hypocalcemia caused by increased phosphorus load, human milk or formulas low in phosphorus and supplementation with calcium are recommended. If associated with hypomagnesemia, serum magnesium should be corrected prior to treating hypocalcemia.

Hypercalcemia. Hypercalcemia is defined as a serum calcium level over 11 mg/dL (2.75 mmol/L) or an ionized calcium level greater than 1.45 mmol/L. Hypercalcemic disorders, such as subcutaneous fat necrosis, Williams's syndrome, congenital hyperparathyroidism, neonatal Bartter's syndrome, osteopetrosis, and familial hypocalciuric hypercalcemia, are all exceedingly rare among newborns. Hypercalcemia is usually iatrogenic and results from excessive administration of calcium or vitamin D, or by insufficient phosphorus intake (human milk). Hence, before embarking on an elaborate differential diagnosis and expensive tests, one should carefully review the actual calcium, phosphorus, and vitamin D intakes.

Secondary hyperparathyroidism may be caused by maternal hypoparathyroidism or hypocalcemia, which leads to high PTH levels in the fetus. This condition is usually transient and resolves completely by 6 months of age. Primary hyperparathyroidism is caused by mutations in the *CASR* gene (Houillier & Paillard, 2003). The type presenting in neonates is familial hypocalciuric hypercalcemia characterized by abnormally low urine calcium and high PTH levels in the presence of an elevated serum calcium.

Clinical signs are nonspecific and include constipation, polyuria, and bradycardia. Infants with long-standing hypercalcemia may present with failure to thrive. Nephrocalcinosis (calcium deposition in the renal parenchyma) and nephrolithiasis (renal stones) accompanied with hematuria are often the earliest presentation of hypercalcemia. Nephrocalcinosis is a common finding in VLBW infants due to the calciuric effects of commonly used drugs such as furosemide. Long-term outcomes for infants with nephrocalcinosis are unknown.

Treatment of hypercalcemia is as follows:

- Calcium and vitamin D supplementation is suspended, and dietary intake of calcium and vitamin D is restricted (human milk or vitamin D–free formula is given).
- Urinary excretion of calcium is promoted by fluid administration (about twice the maintenance requirement).
- In the case of vitamin D excess, glucocorticoids are given to reduce intestinal absorption and bone resorption of calcium.
- As a last resort, pamidronate can be tried, although experience with bisphosphonates in newborns is limited. Pamidronate is generally given at a dose of 1 mg/kg, as a single 4-hour IV infusion. Additional doses are given weekly if necessary as serum calcium nadir occurs by day 6 to 7.
- Dialysis may be needed in case of severe and refractory hypercalcemia.

Phosphorus. Phosphorus is absorbed mainly in the duodenum and jejunum by both active and passive diffusion. Absorption depends on the amount of phosphorus in the diet, the relative concentrations of phosphorus and calcium (excessive calcium can diminish phosphorus absorption and vice versa), and the presence of phosphorus-binding substances (e.g., phytates in soy-based formulas).

The kidneys excrete phosphorus and it is under the control of PTH and fibroblast growth factor (FGF 23) activity. High levels of PTH and FGF 23 lead to hypophosphatemia due to their phosphaturic effects. Normally, about 95% to 99% of the filtered phosphorus is reabsorbed in term infants. Preterm infants have a greater fractional excretion of phosphorus in urine.

Disorders of phosphorus balance are listed in Box 19.5.

Hypophosphatemia. Hypophosphatemia is defined as a serum phosphorus level below 4 mg/dL (1.29 mmol/L) and is a common feature in preterm infants with metabolic bone disease, which is caused by insufficient intake of calcium and phosphorus. Adequate levels of phosphorus are needed to cause apoptosis (programmed cell death) of hypertrophic cells in the bony growth plate. **Quality and Safety: Therefore, hypophosphatemia leads to formation of abnormal bone tissue and metabolic bone disease** (Tiosano & Hochberg, 2009). Phosphorus deficiency can also result in muscle weakness and impaired white cell function.

In very rare cases, hypophosphatemia may be caused by neonatal hyperparathyroidism. In infancy, hypophosphatemia can occur due to disorders of vitamin D metabolism (vitamin D–dependent rickets) or defects in renal phosphorus transport (hypophosphatemic rickets).

Severe hypophosphatemia, a serum phosphorus level below 1 mg/dL (.32 mmol/L), is uncommon and usually occurs only in newborns receiving parenteral alimentation with an inadequate amount of phosphorus. Respiratory failure and decreased myocardial performance have been described as possible consequences of severe hypophosphatemia.

Hyperphosphatemia. Hyperphosphatemia is defined as a serum phosphorus level over 7 mg/dL (2.26 mmol/L) and can be caused by ingestion of milk formulas containing high amounts of phosphorus,

Box 19.5

DISORDERS OF PHOSPHORUS BALANCE

Hypophosphatemia

- Metabolic bone disease
- Inadequate parenteral phosphorus administration
- Malabsorption
- Hyperparathyroidism
- Familial hypophosphatemia: vitamin D–resistant rickets, X-linked hypophosphatemia

Hyperphosphatemia

- Impaired excretion of phosphorus: renal failure
- Hypoparathyroidism
- Excessive parenteral or enteral administration of phosphorus

excessive parenteral administration of phosphorus, impaired phosphorus excretion (renal failure), or by defects in hormonal regulation (hypoparathyroidism). Severe hyperphosphatemia may cause metastatic calcifications and hypocalcemia. Management includes alimentation with human milk or with a low-phosphorus formula, and calcium supplementation to increase binding of phosphorus to promote its fecal excretion. Reducing the parenteral phosphorus intake usually resolves parenteral hyperphosphatemia. In renal failure, 1,25-dihydroxyvitamin D, which exerts its effects independent of functioning renal tissue, can be given to counteract hypocalcemia secondary to hyperphosphatemia.

Supplementation with 1,25-dihydroxyvitamin D and calcium may be used to treat hypoparathyroidism in newborns arising from maternal hyperparathyroidism (transient secondary hypoparathyroidism) or from permanent primary hypoparathyroidism (sporadic or hereditary).

Metabolic Bone Disease. This condition occurs primarily in VLBW infants and is associated with a number of prenatal and postnatal risk factors (Box 19.6). Early initiation of enteral nutrition, use of specialized preterm formulas, and parenteral supplementation of calcium and phosphorus has led to a decrease in the incidence of this disease. The relative calcium, phosphorus, and vitamin D content of commonly used enteral feeds for VLBW infants are given in Table 19.4. Management of metabolic bone disease is centered on maximizing calcium and phosphorus intake. Infants that are unable to tolerate preterm formulas or appropriately fortified human milk require supplementation with elemental calcium at 20 mg/kg/day (up to a maximum of 80 mg/kg/day) and elemental phosphorus at 10 to 20 mg/kg/day (up to a maximum of 50 mg/kg/day). Serum 25-hydroxyvitamin D levels should be maintained above 20 ng/mL and medications like furosemide, dexamethasone, and caffeine should be judiciously used.

Magnesium. Magnesium is distributed primarily in the skeleton and the intracellular space. It is involved in energy production, cell membrane function, mitochondrial function, nerve conduction, and protein synthesis. In the serum, about a third of the magnesium is bound to albumin.

Magnesium is absorbed in the small intestine by both a passive and an active saturable mechanism. Absorption is related to intake, and approximately half of the dietary magnesium is absorbed. The kidneys, under the influence of many hormones, regulate the serum magnesium concentration and normally less than 5% of the filtered magnesium is excreted. PTH, calcitonin, ADH, and insulin increase magnesium reabsorption. The majority of magnesium reabsorption occurs in the ascending limb of the loop of Henle. PTH also mobilizes magnesium from the bone to increase the serum magnesium concentration. An acute decline in the serum magnesium concentration increases secretion of PTH, but chronic magnesium deficiency reduces PTH secretion and may cause hypocalcemia.

The recommended intake for preterm infants is based on placental accretion rates: 8 to 15 mg/kg/day (Agostoni et al., 2010). Magnesium content of mature human milk is about 26 mg/L. In parenteral solutions, its concentration should be maintained between 36 and 48 mg/L to avoid precipitation.

Disorders of magnesium balance are listed in Box 19.7.

TABLE 19.4

CALCIUM, PHOSPHORUS, AND VITAMIN D CONTENT OF ENTERAL FEEDS

	Unfortified Human Milk (20 kcal/oz)	Fortified Human Milk (24 kcal/oz)	Preterm Formula (24 kcal/oz)
Calcium (mg/kg)	37	184–218	210–234
Phosphorus (mg/kg)	21	102–125	107–130
Vitamin D (IU/day)	2.4	283–379	290–468

Note: For 160 mL/kg/day of feeds for an infant weighing 1,500 g.

Source: Adapted from Martin, R. J., Fanaroff, A. A., & Walsh, M. C. (Eds.). (2015). *Fanaroff and Martin's neonatal-perinatal medicine: Diseases of the fetus and infant* (10th ed.). Philadelphia, PA: Saunders.

Box 19.6

RISK FACTORS FOR METABOLIC BONE DISEASE

Prenatal

- Premature birth: abrupt cessation of placental calcium and phosphorus accretion
- Intrauterine growth restriction
- Preeclampsia
- Maternal vitamin D deficiency

Postnatal

- Inadequate intake of calcium and phosphorus
- Medications: diuretics, methylxanthines, steroids
- Vitamin D deficiency
- Sedation or paralysis

Box 19.7

DISORDERS OF MAGNESIUM BALANCE

Hypomagnesemia

- Infant of diabetic mother
- Intrauterine growth restriction
- Malabsorption syndromes
- Loop diuretics and aminoglycosides
- Isolated renal magnesium wasting

Hypermagnesemia

- Maternal treatment with $MgSO_4$ (e.g., for tocolysis, preeclampsia)
- Excessive magnesium administration with parenteral nutrition
- Magnesium-containing antacids
- Magnesium therapy for neonatal pulmonary hypertension

$MgSO_4$, magnesium sulfate.

Hypomagnesemia. Hypomagnesemia is defined as a serum magnesium level below 1.6 mg/dL (0.66 mmol/L). Hypomagnesemia may be a cause or the effect of neonatal hypoparathyroidism. Magnesium transfer from the mother to the fetus is impaired in maternal disorders with placental insufficiency and predisposes neonates to hypomagnesemia. Infants of diabetic mothers have an increased incidence of hypomagnesemia as a consequence of maternal magnesium depletion (Banerjee et al., 2003). **Emergency Alert: Loop diuretics and aminoglycosides have been associated with renal magnesium wasting.** Isolated defects of intestinal malabsorption and renal wasting of magnesium have also been described.

Symptoms of hypomagnesemia are usually not apparent until the levels fall below 1.2 mg/dL (0.49 mmol/L). The symptoms of hypomagnesemia are similar to hypocalcemia and frequently coexist in clinical practice. Neonatal hypomagnesemia is usually benign and transient (except in cases of malabsorption and renal wasting). It can cause hyperexcitability, tremors, and, occasionally, severe hypocalcemic seizures that are unresponsive to anticonvulsant medications and calcium replacement. They respond to slow infusion of 0.1 mL/kg of 50% magnesium sulfate ($MgSO_4$). **Emergency Alert: Complications include systemic hypotension and arrhythmias.** Treatment can be repeated with close monitoring of the serum magnesium concentration every 12 hours, until normal magnesium levels are achieved. In cases of malabsorption syndromes, daily oral supplementation of 1 mL/kg of 50% $MgSO_4$ may be required.

Hypermagnesemia. Hypermagnesemia is defined as a serum magnesium level over 2.8 mg/dL (1.15 mmol/L). Hypermagnesemia is usually secondary to excessive administration through parenteral nutrition or following maternal treatment with $MgSO_4$ for tocolysis, neuroprotection, or seizure prevention in preeclampsia. Serum levels following maternal treatment seldom reach dangerous levels and gradually return to normal after several days. Rarely, magnesium-containing antacids and treatment of persistent pulmonary hypertension of the newborn with $MgSO_4$ can cause hypermagnesemia.

The most common presentation of hypermagnesemia is perinatal depression of the infant following maternal magnesium therapy. Clinical signs include hyporeflexia, lethargy, and respiratory depression. Hypermagnesemia can lead to a decrease in PTH and 1,25-dihydroxyvitamin D production resulting in a fall in serum calcium concentration. Treatment of hypermagnesemia is usually supportive. It is important to maintain adequate hydration to promote urinary excretion. Loop diuretics may also be used to aid renal elimination. Rarely, mechanical ventilation may be required to overcome respiratory depression.

ACID–BASE BALANCE

A number of complex physiologic processes are at work in a normal infant to maintain the pH within a tight range of 7.35 to 7.45. This pH range is essential for normal metabolic functioning, growth, and development. These processes are disrupted in critically ill neonates and preterm infants, leading to either acidosis or alkalosis. Preterm infants are especially at risk for acidosis due to their impaired renal ability to acidify urine and lower renal threshold for bicarbonate absorption compared to term infants.

The following are the two main processes that help maintain acid–base balance.

Acute Compensation

Whenever acute changes in the acid–base status occur, there are two major buffering mechanisms that come into play to restore pH to normal levels. First, the H^+/K^+ exchanger can alter the relative concentrations of H^+ and K^+ in the intracellular and extracellular spaces. For example, when there is acidosis (decrease in serum pH), this exchanger causes the H^+ ions to move intracellularly and K^+ to move extracellularly. Hence, acute acidosis is often complicated and accompanied by hyperkalemia. The second buffering mechanism is via carbonic anhydrase, an enzyme that catalyzes the conversion of water (H_2O) and carbon dioxide (CO_2) to carbonic acid (H_2CO_3) and vice versa. The H_2CO_3 can dissociate to form H^+ and HCO_3^- ions.

CO_2 crosses the blood–brain barrier and decreases the pH, resulting in activation of central chemoreceptors that increase the respiratory drive and lead to CO_2 excretion. Similarly, alkalosis results in hypoventilation, leading to retention of CO_2 in an attempt to normalize the pH. It is important to note that respiratory compensatory mechanisms can only partially normalize serum pH. Hence, if the serum pH is normal, a mixed acid–base disorder should be suspected rather than a compensated condition.

Long-Term Compensation

The lungs and kidneys are responsible for maintenance of long-term acid–base homeostasis. The lungs primarily excrete CO_2, a by-product of energy metabolism. The kidneys excrete a daily acid load of about 1 to 2 mEq/kg and more in pathologic processes such as sepsis or lactic acidosis. The kidneys also maintain acid–base balance by reabsorption and excretion of bicarbonate, which may be disrupted in conditions such as RTA.

Metabolic Acidosis

Metabolic acidosis is defined as a serum pH of less than 7.30 with a normal P_{CO_2} level and decreased HCO_3^- level. It is a common finding in preterm and critically ill neonates. It is divided into two categories based on anion gap: (a) increased anion gap metabolic acidosis and (b) normal anion gap metabolic acidosis (Box 19.8). Anion gap is defined as the difference between the measured cations (positively charged ions) and anions (negatively charged ions) in the serum. It can be calculated by the formula:

$$\text{Anion gap} = (Na^+ + K^+) - (Cl^- + HCO3^-).$$

Normal anion gap is 8 to 16 mEq/L

The most common cause of increased anion gap metabolic acidosis is lactic acidosis. Endogenous lactic acid, a by-product of

Box 19.8

CAUSES OF METABOLIC ACIDOSIS

Increased Anion Gap

- Sepsis, necrotizing enterocolitis
- Hypoxia
- Hypovolemic shock
- Inborn errors of metabolism (organic acidemia, glycogen storage disease, galactosemia, mitochondrial defects)
- Maternal salicylate use

Normal Anion Gap

- Renal tubular acidosis
- Secretory diarrhea
- Carbonic anhydrase inhibitors (e.g., acetazolamide, dorzolamide)

anaerobic metabolism, is produced in conditions with poor tissue perfusion as seen in sepsis, hypoxia, or NEC. Acidosis with increased anion gap can also be seen in the case of inborn errors of metabolism like organic acidemias, glycogen storage disease, galactosemia, or mitochondrial defects. A condition unique to neonates is the *late metabolic acidosis* of prematurity. It is usually seen in the third week of life and is caused by the excess acid load following the use of high protein (casein/whey) formulas. This is mostly a self-limited condition and resolves as the kidneys mature.

Normal anion gap metabolic acidosis is commonly seen in RTA, diarrhea, and with certain medications. In proximal RTA (type II), there is a defect in the bicarbonate reabsorption, while in distal RTA (type I), there is an inability to excrete H^+ ion. In diarrhea, there is an excessive loss of HCO_3^- ion in the stool. Medications like carbonic anhydrase inhibitors cause decreased uptake of HCO_3^- in the kidneys. In order to maintain electrical neutrality, the serum chloride level is usually elevated in normal anion gap metabolic acidosis.

Treatment is aimed at correcting the underlying cause. Bicarbonate should be used with extreme caution as it can inadvertently increase P_{CO_2}, with a consequential shift in the oxyhemoglobin dissociation curve to the left, leading to decreased oxygen delivery to the tissues and intracellular acidosis.

Metabolic Alkalosis

Metabolic alkalosis is defined as a serum pH greater than 7.45 with a normal P_{CO_2} level and elevated HCO_3^- level. The most common cause of metabolic alkalosis in preterm infants is chronic diuretic therapy for BPD. Depletion of the extracellular fluid volume leads to metabolic alkalosis by activation of the renin–angiotensin–aldosterone system leading to Na^+ absorption and H^+ and K^+ excretion in the renal tubules. Volume depletion also reduces the GFR and thus the amount of bicarbonate filtered. This is termed as contraction alkalosis. Metabolic alkalosis is divided into two categories (Box 19.9): (a) chloride responsive and (b) chloride resistant. A urinary chloride level can help delineate the type.

Chloride-responsive metabolic alkalosis is associated with a low urinary chloride level and is seen after chronic diuretic therapy (furosemide acts by inhibiting the Na^+-K^+-Cl^- cotransporter), excessive loss of gastric hydrochloric acid due to vomiting or prolonged nasogastric aspiration, and congenital chloride-wasting diarrhea (rare).

Chloride-resistant metabolic alkalosis is associated with a high urinary chloride level and is seen in early diuretic therapy; excessive administration of bicarbonate, acetate, or citrate; and Bartter's syndrome (rare).

Mild to moderate metabolic alkalosis does not warrant therapy. Treatment is aimed at correcting the underlying cause. Metabolic alkalosis secondary to chronic diuretic therapy is treated by supplementing chloride in the form of KCl either enterally or parenterally. Discontinuation or alteration of the diuretic dose may also be required. Alkalosis due to loss of gastric acid is corrected by appropriate fluid replacement (normal saline or Ringer's lactate). Acetazolamide has been occasionally used for treatment in critically ill neonates but the evidence is limited (Andrews, Johnson, Lammers, Harrison, & Miller, 2013).

Box 19.9

CAUSES OF METABOLIC ALKALOSIS

Chloride Responsive

- Chronic diuretic therapy
- Loss of gastric acid (nasogastric suction or vomiting)
- Congenital chloride diarrhea

Chloride Resistant

- Early diuretic therapy
- Excessive administration of base (bicarbonate, acetate, or citrate)
- Bartter's syndrome

Respiratory Acidosis

Respiratory acidosis is an increase in P_{CO_2} associated with a decrease in serum pH. It is caused by conditions that decrease the respiratory drive (ventilation) leading to CO_2 retention. The most common causes are RDS, transient tachypnea of newborn (TTN), pneumonia, meconium aspiration, and chronic lung disease. It can also be seen acutely in an obstructed or improperly positioned endotracheal tube. A strategy of permissive hypercapnia (respiratory acidosis) is often used in infants with chronic lung disease to minimize ventilator-associated lung injury and facilitate weaning of respiratory support.

Respiratory Alkalosis

Respiratory alkalosis is a decrease in P_{CO_2} associated with an increase in serum pH. The most common cause of respiratory alkalosis in neonates is mechanical overventilation. A factitious decrease in P_{CO_2} is also observed whenever an air bubble is trapped in the blood gas specimen. True central hyperventilation (increased respiratory rate) requires further diagnostic workup as it is associated with intracranial pathologies and hyperammonemia.

Identifying Acid–Base Disturbances

When one of the four conditions mentioned earlier is present in isolation, it is called a simple acid–base disorder. In these conditions, an appropriate respiratory or renal compensation occurs to counteract the primary abnormality to mitigate large changes in the serum pH. For example, a primary metabolic acidosis is associated with a respiratory compensation wherein P_{CO_2} levels decrease and respiratory alkalosis ensues. Similarly, a primary respiratory acidosis is associated with compensatory renal changes (increase in secretion of H^+ ion) that lead to metabolic alkalosis. The respiratory compensation of primary metabolic abnormalities occurs rapidly, while metabolic compensation for a primary respiratory acid–base disorder occurs more slowly. There is an initial acute but modest response followed by a chronic renal response that usually takes 3 to 5 days. If the compensation in pH from a respiratory or renal process is greater or lesser than expected, a mixed acid–base disorder is suspected. For example, in a septic patient with metabolic acidosis due to poor perfusion, there may be associated respiratory failure leading to respiratory acidosis and a higher than expected P_{CO_2} level. Appropriate diagnosis of acid–base disturbances requires (a) identification of the primary abnormality (history, clinical examination, and laboratory data) and (b) assessment of the degree of secondary compensation. The expected values for appropriate secondary compensation for the various disorders are given in Table 19.5 (Adrogue & Madias, 2010).

Nursing Management

Nurses have a vital role to play in the fluid and electrolyte management of infants admitted to the NICU. In addition to obtaining

TABLE 19.5

COMPENSATORY RESPONSE TO PRIMARY ACID–BASE DISTURBANCES

Acid–Base Disturbance	Primary Finding	Secondary Compensation
Metabolic acidosis	Every 1 mEq/L decrease in HCO_3^-	Decrease in Pco_2 by 1.2 mmHg
Metabolic alkalosis	Every 1 mEq/L increase in HCO_3^-	Increase in Pco_2 by 0.7 mmHg
Respiratory acidosis	Every 10 mmHg increase in Pco_2	Acute: increase in HCO_3^- by 1 mEq/L Chronic: increase in HCO_3^- by 4 mEq/L
Respiratory alkalosis	Every 10 mmHg decrease in Pco_2	Acute: decrease in HCO_3^- by 2 mEq/L Chronic: decrease in HCO_3^- by 4 mEq/L

vital signs and monitoring intake–output and daily weights, they are responsible for securing peripheral and central vascular access to ensure the safe delivery of IV fluids and medications. **Quality and Safety: It is crucial for a bedside nurse to promptly recognize and report the signs and symptoms of fluid and electrolyte imbalance to avoid complications associated with inappropriate fluid administration.**

Assessment and Evaluation in Fluid and Electrolyte Therapy. The estimation of an infant's fluid and electrolyte needs depends on the gestational age, day of life, weight, and the underlying disease process. The needs of a 4-kg infant with perinatal asphyxia and seizures are vastly different from those of a 32-week, 1,750 g infant with RDS or a 24-week, 500 g infant with multiple complex problems. Each represents a different disease process along with varying degrees of organ maturation necessitating careful management of fluid and electrolytes to maintain homeostasis.

Fluid Requirement. Fluid needs of an infant can be calculated using body weight, body surface area, or caloric expenditure (Behrman, Kleigman, & Jenson, 2011). In clinical practice, the total daily fluid requirement is approximated based on the gestational age, weight, and the day of life of an infant. It is then further adjusted by accounting for past and projected losses. Factors that impact water loss in neonates are given in Table 19.1. An example of this is the term newborn infant with a large gastroschisis. This midline abdominal wall defect predisposes the infant to large IWLs because of the exposed abdominal organs. Similarly, a 24-week, 500 g infant with the typical "translucent" skin that has not yet formed a competent epidermal barrier is predisposed to dehydration due to large IWL through the skin. The fluid requirements for such an infant may be as high as 150 to 200 mL/kg/day. In contrast, a birth-asphyxiated full-term infant may need fluids restricted to no more than 40 to 50 mL/kg/day for the first 48 to 72 hours of life.

Environmental factors such as temperature and humidity also affect IWL. The use of radiant warmers increases IWL, while the use of a double-walled, well-humidified incubator significantly reduces the IWL. Finally, it is critical for a nurse to double-check fluid orders to ensure that the correct fluids and rate are delivered. The approximate maintenance requirements of newborns in the first week of life (based on birthweight) are given in Table 19.2.

Fluid Output. The underlying disease process dictates the frequency of fluid (intake–output) calculations, which are usually performed once a day. In neonates recovering from acute renal failure (polyuric phase), calculations may need to be done every 4 hours, whereas in conditions with decreased urine output (renal failure, nephrotoxic drugs) it may suffice to calculate every 12 to 24 hours. Urine output is measured and expressed in mL/kg/hour and, if less than 1 mL/kg/hour, the infant is diagnosed to have oliguria.

For example, if a 32-week gestation 2-kg infant has 240 mL of urine in a 24-hour period,

$$\text{UOP} = 240 \text{ mL}/24 \text{ hour} = 10 \text{ mL/hour}$$

$$10 \text{ mL/hour} / 2 \text{ kg} = 5 \text{ mL/kg/hour}$$

This is an adequate UOP for an infant of this weight and gestational age.

Neonates can also have significant fluid losses through vomiting, diarrhea, ostomy, nasogastric tube, chest tube, and surgical wound drainage. In general, if the fluid loss from these sources exceeds 20 mL/kg in 24 hours, replacement fluids should be initiated to prevent fluid and electrolyte imbalance. Table 19.3 gives the electrolyte concentrations of different body fluids and can be used to guide the choice of replacement fluids.

Infant Weight. Weight is a sensitive indicator of overall fluid status. Infants are usually weighed daily; however, extremely low birth weight (ELBW) infants are weighed more often (i.e., every 12 hours) as fluid requirements are recalculated on the basis of weight changes. It is important to weigh infants accurately, as inaccuracies can lead to wrong calculations and detrimental outcomes. Neonates should be weighed nude, with minimal extraneous equipment (e.g., EKG leads, probes), at the same time each day, and on the same scale. In-bed scales that give constant weight readouts simplify the weighing process and reduce infant stress. Birth weight is used to calculate daily fluid requirements during the first week of life as physiologic fluid shifts occur and impact daily weights. Once the infant regains birth weight, the daily weights are used to calculate fluid needs.

Physical Examination. The physical examination can reveal changes in the infant's fluid status and should be used in conjunction with laboratory data to plan interventions in fluid and electrolyte therapy. A general assessment of hydration status includes the infant's color, skin turgor, activity, mucous membranes, fontanelles, and capillary refill:

- *Color:* Pink and well perfused, rather than pale and mottled (indicates dehydration)
- *Skin turgor:* Good turgor, rather than "tenting" (indicates dehydration) or edematous and shiny (indicates fluid overload)
- *Activity:* Active with good tone, rather than lethargic and hypotonic (indicates dehydration or overhydration)
- *Mucous membranes:* Pink and moist, rather than dry and gray (indicates dehydration)
- *Fontanelles:* Soft and flat, rather than depressed (indicates dehydration) or tense and full (may indicate overhydration)
- *Capillary refill:* It is an important indicator of peripheral perfusion and hydration status. Normal capillary refill time in neonates is less than or equal to 2 seconds. Capillary refill greater than 3 seconds is concerning for dehydration.

Vital Signs

Heart Rate: Tachycardia is a relatively early sign of dehydration. As a variety of other factors can also cause tachycardia in neonates (pain, anemia, or caffeine therapy), the heart rate trend is more useful in diagnosing fluid imbalance rather than absolute values.

Blood Pressure: Hypotension and shock occur late in dehydration. Acute changes in the mean arterial blood pressure are a significant risk factor for IVH in extremely preterm neonates (Bada et al., 1990).

Laboratory Data. The frequency of laboratory assessment depends on the clinical status of the infant. In most preterm and critically ill infants that require intravenous fluids, a daily basic metabolic panel (BMP) is obtained for the first 3 days of life. These assessments are made more frequently in infants with high fluid losses or with significant derangements in electrolytes. On the other hand, infants with relatively stable electrolytes despite being on chronic diuretic therapy may only require weekly checks.

Point-of-care assessment of urine specific gravity (normal 1.005–1.012) and acute changes in central hematocrit are also helpful in assessing hydration status at the bedside.

SUMMARY

The care of infants with alterations in fluid and electrolyte balance presents a management challenge for both physicians and nurses. A thorough understanding of the underlying pathophysiology and the rationale for therapy enables the healthcare team to provide more informed care for these infants and to anticipate and prevent problems.

CASE STUDY

A 24-week female infant with a birth weight of 500 g was born to a 30-year-old gravida 1 para 1 mother following preterm labor. Pregnancy was complicated by limited prenatal care, and maternal group B streptococcus status is unknown. The delivery occurred via a caesarian section under general anesthesia. Upon delivery, the infant was limp, blue, and apneic and required intubation and mechanical ventilation. Apgar scores were 2, 6, and 8 at 1, 5, and 10 minutes, respectively. Upon arrival to the NICU, the nurse obtains peripheral IV access and screening septic workup is drawn. Umbilical venous and arterial lines are placed and the infant is given a dose of ampicillin and gentamicin. Infant is started on a $D_{7.5}W$ with amino acids at 80 mL/kg/day. Vital signs remain stable and a BMP obtained at 24 hours of life is normal. Venous blood gas is pH 7.26, P_{CO_2} 49 mmHg, and base deficit of –5. Bilirubin level is noted to be 8 mg/dL and the infant is started on phototherapy. On day of life (DOL) 2, the infant's fluid goal is increased to 100 mL/kg/day and 1/4 sodium acetate is added to fluids, but she loses peripheral access. The nurse also reports concerns with the umbilical venous line fluids repeatedly backing up and notices that the bed is soaked with clear fluid. Following this, a peripherally inserted central catheter (PICC) is placed by the nurse and IV fluids are restarted at the previous rate. A BMP obtained on DOL 3 shows Na^+ 161 mEq/L, K^+ 6.5 mEq/L, Cl^- 129 mEq/L, $HCO3^-$ 16 mEq/L, BUN 53 mg/dL, creatinine 1.26 mg/dL, glucose 73 mg/dL, and serum osmolality 345 mOsm/L.

■ Differential Diagnoses for Hypernatremia

- Dehydration due to peripheral/central line malfunction (umbilical venous line repeatedly backing up with clear fluid soaking the bed, lack of intravenous fluids while PICC was being attempted)
- Excessive IWL due to immature skin and phototherapy (24-week infant with high bilirubin)
- Excessive administration of sodium (addition of 1/4 sodium acetate to fluids on DOL 2)

■ Assessment

Weight: Birth weight 500 g, weight on DOL 2, 450 g. 10% weight loss.

Vital signs: Heart rate 180 beats/minute; respiratory rate 60 breaths/minute; blood pressures: systolic 40 mmHg, diastolic 18 mmHg; mean arterial pressure 25 mmHg.

■ Physical Examination

- GENERAL: decreased spontaneous activity
- HEENT: normocephalic, anterior fontanelle slightly sunken
- RESPIRATORY: bilateral breath sounds equal and clear
- CARDIOVASCULAR: tachycardia with continuous murmur; pulses = +1; capillary refill ~3 seconds
- ABDOMEN: soft, round, and not tender to palpation, no hepatosplenomegaly noted
- GENITOURINARY: immature female genitalia
- SKIN: immature skin with developing areas of breakdown

■ Diagnostic Tests

- BMP
- Serum osmolality
- Urine specific gravity
- Blood gas
- Complete blood count

■ Development of Management Plan

The management plan involves evaluating the fluid status based on clinical examination and laboratory data. This extremely premature infant has lost 10% of birth weight on DOL 2, and on physical examination has signs concerning for dehydration. BMP on DOL 3 shows increased serum osmolality, hypernatremia, hyperkalemia, hyperchloremia, and metabolic acidosis. The most likely cause of hypernatremia is dehydration due to cessation of intravenous fluid delivery secondary to loss of peripheral and central venous access. Furthermore, a fluid goal of 80 to 100 mL/kg/day in the first 48 hours of life is inadequate for this ELBW infant weighing only 500 g due to high IWL through the immature skin. Phototherapy is an additional risk factor that augments the IWLs. Early sodium supplementation in the absence of adequate diuresis can increase the risk for hypernatremia.

The total fluid goal for this infant should be increased by about 40 to 60 mL/kg/day to correct dehydration. **Quality and Safety: Normal saline boluses should be avoided as ELBW infants at this age have poor cerebral blood flow autoregulation and are at significant risk for IVH. The incubator temperature and humidity should be set to maintain a thermoneutral environment.**

■ Evaluation of Intervention

Periodic assessment of the infant's weight, vital signs, and physical examination are critical. A BMP is repeated to evaluate the electrolytes 12 to 24 hours later. The correction of sodium levels should not be greater than 10 to 12 mEq/L/day (or 0.5 mEq/L/hour), due to the risk for cerebral edema. The infant is also monitored for signs of hyperkalemia and metabolic acidosis.

■ Outcome

After the fluid goal was readjusted and measures were taken to reduce IWL, the electrolyte abnormalities slowly corrected over a 48-hour period.

EVIDENCE-BASED PRACTICE BOX

Virtually all preterm infants need intravenous fluid infusions for a variable length of time, depending on the degree of prematurity and severity of complications. The optimal daily fluid requirements are tailored to the infant's needs. In 2014, Bell and Acarregui published a meta-analysis to determine the effect of varying levels of fluid intake on postnatal weight loss, morbidity, and mortality in preterm infants. Five randomized controlled trials evaluating different intravenous fluid intakes were included in the analysis.

The water intake in the "Restricted Fluids" group ranged from 50 to 122 mL/kg/day, while in the "Liberal Fluids" group it ranged from 80 to 169 mL/kg/day. The postnatal weight loss was significantly higher, along with a trend toward increased risk of dehydration in the fluid-restricted group. The risk of PDA (relative risk, RR, 0.52 and number needed to treat, NNT, was 7) and NEC (RR 0.43 and NNT was 20) was significantly lower in the fluid-restricted group. In addition, there was a trend toward reduced risk of chronic lung disease and IVH in the fluid-restricted group but it did not reach statistical significance. There was no difference in mortality between the two groups.

The authors concluded that appropriately restricted fluid intake (without causing dehydration) in preterm neonates could potentially reduce the risk of PDA and NEC.

Reference

Bell, E. F., & Acarregui, M. J. (2014). Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants. *The Cochrane Database of Systematic Reviews*, (12), CD000503. doi:10.1002/14651858.CD000503.pub3

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ONLINE RESOURCES

Ambalavanan, N. (2018). Fluid, electrolyte, and nutrition management of the newborn. In D. J. Nimavat (Ed.), *Medscape*. Retrieved from https://emedicine.medscape.com/article/976386-overview

Anion Gap Calculator. Retrieved from https://www.mdcalc.com/anion-gap

Cochrane Neonatal. Retrieved from https://neonatal.cochrane.org/welcome

National Center for Education in Maternal and Child Health. Retrieved from http://www.ncemch.org

Sodium Deficit in Hyponatremia. Retrieved from https://www.mdcalc.com/sodium-deficit-hyponatremia

REFERENCES

Abrams, S. A. (2013). Calcium and vitamin D requirements of enterally fed preterm infants. *Pediatrics, 131*(5), e1676–1683. doi:10.1542/peds.2013-0420

Adrogue, H. J., & Madias, N. E. (2010). Secondary responses to altered acid–base status: The rules of engagement. *Journal of the American Society of Nephrology, 21*(6), 920–923. doi:10.1681/asn.2009121211

Agostoni, C., Buonocore, G., Carnielli, V. P., De Curtis, M., Darmaun, D., Decsi, T., . . . Ziegler, E. E. (2010). Enteral nutrient supply for preterm infants: Commentary from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition. *Journal of Pediatric Gastroenterology and Nutrition, 50*(1), 85–91. doi:10.1097/MPG.0b013e3181adaee0

Andrews, M. G., Johnson, P. N., Lammers, E. M., Harrison, D. L., & Miller, J. L. (2013). Acetazolamide in critically ill neonates and children with metabolic alkalosis. *Annals of Pharmacotherapy, 47*(9), 1130–1135. doi:10.1177/1060028013500468

Bada, H. S., Korones, S. B., Perry, E. H., Arheart, K. L., Ray, J. D., Pourcyrous, M., . . . Tullis, K. V. (1990). Mean arterial blood pressure changes in premature infants and those at risk for intraventricular hemorrhage. *The Journal of Pediatrics, 117*(4), 607–614. doi:10.1016/s0022-3476(05)80700-0

Banerjee, S., Mimouni, F. B., Mehta, R., Llanos, A., Bainbridge, R., Varada, K., & Sheffer, G. (2003). Lower whole blood ionized magnesium concentrations in hypocalcemic infants of gestational diabetic mothers. *Magnesium Research, 16*(2), 127–130.

Baraton, L., Ancel, P. Y., Flamant, C., Orsonneau, J. L., Darmaun, D., & Roze, J. C. (2009). Impact of changes in serum sodium levels on 2-year neurologic outcomes for very preterm neonates. *Pediatrics, 124*(4), e655–e661. doi:10.1542/peds.2008-3415

Baumgart, S., & Costarino, A. T. (2000). Water and electrolyte metabolism of the micropremie. *Clinics in Perinatology, 27*(1), 131–146, vi–vii. doi:10.1016/s0095-5108(05)70010-5

Behrman, R. E., Kleigman, R., & Jenson, H. B. (2011). *Nelson textbook of pediatrics* (19th ed.). Philadelphia, PA: WB Saunders.

Bell, E. F., Warburton, D., Stonestreet, B. S., & Oh, W. (1979). High-volume fluid intake predisposes premature infants to necrotising enterocolitis. *The Lancet, 2*(8133), 90. doi:10.1016/s0140-6736(79)90135-1

Bell, E. F., Warburton, D., Stonestreet, B. S., & Oh, W. (1980). Effect of fluid administration on the development of symptomatic patent ductus arteriosus and congestive heart failure in premature infants. *New England Journal of Medicine, 302*(11), 598–604. doi:10.1056/nejm198003133021103

Bhatia, J. (2006). Fluid and electrolyte management in the very low birth weight neonate. *Journal of Perinatology, 26*(Suppl. 1), S19–S21. doi:10.1038/sj.jp.7211466

Elrefae, F., Elhassanien, A. F., & Alghiaty, H. A. (2013). Congenital chloride diarrhea: A review of twelve Arabian children. *Clinical and Experimental Gastroenterology, 6*, 71–75. doi:10.2147/ceg.s40620

Houillier, P., & Paillard, M. (2003). Calcium-sensing receptor and renal cation handling. *Nephrology Dialysis Transplantation, 18*(12), 2467–2470. doi:10.1093/ndt/gfg420

Lorenz, J. M., Kleinman, L. I., Ahmed, G., & Markarian, K. (1995). Phases of fluid and electrolyte homeostasis in the extremely low birth weight infant. *Pediatrics, 96*(3, Pt. 1), 484–489. Retrieved from https://pediatrics.aappublications.org/content/96/3/484

Maisels, M. J., & McDonagh, A. F. (2008). Phototherapy for neonatal jaundice. *New England Journal of Medicine, 358*(9), 920–928. doi:10.1056/NEJMct0708376

Martin, R. J., Fanaroff, A. A., & Walsh, M. C. (Eds.). (2015). *Fanaroff and Martin's neonatal-perinatal medicine: Diseases of the fetus and infant* (10th ed.). Philadelphia, PA: Saunders.

Modi, N. (2003). Clinical implications of postnatal alterations in body water distribution. *Seminars in Neonatology, 8*(4), 301–306. doi:10.1016/s1084-2756(03)00043-5

Rodriguez-Soriano, J. (1998). Bartter and related syndromes: The puzzle is almost solved. *Pediatric Nephrology, 12*(4), 315–327. doi:10.1007/s004670050461

Tiosano, D., & Hochberg, Z. (2009). Hypophosphatemia: The common denominator of all rickets. *Journal of Bone and Mineral Metabolism, 27*(4), 392–401. doi:10.1007/s00774-009-0079-1

Tsang, R. C., Lucas, A., Uauy, R., & Zlotkin, S. (2005). *Nutritional needs of the preterm infant: Scientific basis and practical guidelines*. Cincinnati, OH: Digital Educational Publishing.

Van Marter, L. J., Leviton, A., Allred, E. N., Pagano, M., & Kuban, K. C. (1990). Hydration during the first days of life and the risk of bronchopulmonary dysplasia in low birth weight infants. *The Journal of Pediatrics, 116*(6), 942–949. doi:10.1016/s0022-3476(05)80658-4

CHAPTER 20

Nutrition Management of Premature Infants

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INTRODUCTION

Meeting the nutritional needs of premature and sick infants is essential to their survival (Heird, Driscoll, Schullinger, Grebin, & Winters, 1972). Under conditions of total starvation, these infants have reserves for only 4.5 days, and daily provision of intravenous glucose will prolong survival for only about 7 days. Therefore, the mandate is to meet the basic nutrient requirements of these infants and to understand their metabolic limitations to avoid physiologic stress and morbidity related to the delivery of enteral and parenteral nutrition (PN). Nutrition management of the premature infant continues shortly after birth with intravenous fluids, PN, and/or enteral feedings depending on the infant's gestational age and clinical condition. The goal is for the premature infant to grow at the same rate and composition as a fetus of the same gestational age without imposing undue metabolic stress (American Academy of Pediatrics [AAP] Committee on Nutrition, 2014c). The goal for the premature infant differs from that of the healthy term infant who is breastfeeding. The premature infant has increased nutrient demands and will require fortification of human milk to meet nutrient needs. Due to illness and immaturity, PN and gavage feedings will be needed. Premature infants are at nutrition risks for many reasons, including early birth, which limits nutrient stores such as calcium, iron, and fat; rapid growth, which increases nutrient demand; illness, which may alter nutrient need, nutrient tolerance, and feeding modality; immature gastrointestinal tract, which presents as decreased gut motility, decreased digestive abilities, and decreased tolerance of feedings; and cold stress increasing energy demand.

After birth, infants lose weight due to fluid losses and low nutrient intakes. Once birth weight is regained, the premature infant will gain weight at the intrauterine rate of 15 g/kg/day and parallel their birth weight curve. By discharge, many infants will have a weight less than the 10th percentile for their postmenstrual age and be classified as extrauterine growth restriction (EUGR; Ehrenkranz, 2010). Improved nutrition during week 1 of life has been associated with better weights at discharge and improved developmental outcomes at 18 months corrected age (Stephens et al., 2009; Valentine et al., 2009). Nutrition and a neonate's nutritional status impact the growth patterns—both immediate and long term. Evidence is mounting to support the need for good nutrition for the premature or sick neonate if short- and long-term complications are to be minimized.

This chapter starts with a brief review of the metabolism of nutrients, minerals, and vitamins in the neonate. It then discusses the developmental and physiologic issues that are unique to the premature and sick infant. A discussion of neonatal nutrition with special emphasis on the premature infant describes the challenges of providing appropriate nutrients. The various nutrition routes are included.

NUTRIENTS

Protein

Protein must be broken down into amino acids to be absorbed. Protein digestion and absorption take place in the stomach, small intestinal lumen, and the intestinal cell, the enterocyte (Neu, 2017). Protein digestion begins in the stomach by gastric acid, hydrochloric acid, and the enzyme pepsin. Protein digestion continues in the intestinal lumen by the presence of pancreatic enzymes. Protein is now in the form of peptides (group of amino acids). In the enterocyte, the peptides are further broken down to amino acids. The amino acids and some small peptides are then absorbed into the blood. The intestine of the infant is immature, and intact proteins can cross into the bloodstream and perhaps induce an allergic reaction to milk protein. The openness of the intestine wall to intact protein is greater with infants born at less than 33 weeks' gestation, but closure does occur a few days after birth (Neu, 2017). In the fetus, gastric acid production has been found at 13 weeks' gestation, and gastric levels are lower in premature infants than levels seen in term infants. Gastric enzymes appear at 16 weeks' gestation and pancreatic enzymes by 24 weeks' gestation. Protein digestion and absorption does not appear impaired with premature infants (Neu, 2017).

Fat

Food fat is mainly present as triglycerides that are three fatty acids attached to the carbohydrate, glycerol. Fat is digested in a two-step process in the intestine. The first step is to make the triglyceride water soluble with the mixing of bile salts from the liver. The second step breaks the triglyceride into two fatty acids and a monoglyceride by the pancreatic lipases, lingual lipase, gastric lipase, intestinal lipase, or milk bile acid stimulated lipase present in human milk. The monoglyceride and free fatty acids can be directly absorbed

into the enterocyte or enter by transporter protein for fatty acids (Neu, 2017). Once in the enterocyte, triglycerides are made and are grouped with cholesterol, lipoproteins, and other lipids to form chylomicrons. The chylomicrons circulate by the lymphatic system into the blood system and then into cells throughout the body. Fat digestion and absorption are limited in infants due to decreased levels of bile salts and lipase levels. Bile acid levels are low due to decreased syntheses and decreased intestinal reabsorption. Fetal lipase levels are detected at 21 weeks' gestation, but do not reach adult concentrations until 6 months of age in the term infant. Premature infants have lower lipase levels at birth than term infants. Fat is 40% to 50% of the dietary calories from human milk or infant formula, so it is a major component of intake by infants for their growth.

Medium chain triglyceride (MCT) oil has been added to premature infant formulas. MCT oils do not require bile salts or pancreatic lipases to be digested and are absorbed directly into the bloodstream by the infant. The addition of MCT does not help the premature infant absorb more fat, but may be helpful for infants with major absorption problems such as infants with short gut syndrome.

Carbohydrate

Carbohydrate must be in its simple form or as monosaccharides to be absorbed. Lactose is the major carbohydrate in human milk and is composed of the monosaccharides glucose and galactose. Starch consists of glucose polymers, and sucrose contains glucose and fructose. Digestion of carbohydrate begins in the mouth with salivary amylase to break it down to smaller-size carbohydrates or oligosaccharides. The digestion continues with human milk alpha-amylase when consumed and pancreatic amylase enzymes in the intestine. The final digestion occurs on the brush border of the enterocyte with the enzymes lactase, maltase, and sucrase used to break down lactose, starch, and sucrose. The monosaccharides are carried into the enterocyte by a transport protein and into the blood by a different transport protein. Premature infants have decreased levels of the enzymes lactase, maltase, and sucrase, but after birth with lactose-containing human milk, the lactase enzymes are increased by 2 weeks of age (Neu, 2017). Formulas for premature infants contain a blend of lactose and glucose polymers that are well tolerated. Infants who have intestinal damage following necrotizing enterocolitis (NEC) or have developed short gut syndrome may not tolerate lactose and will need a formula containing glucose polymers (corn syrup solids).

Summary

The absorption of the three major nutrients is relatively inefficient in the preterm as well as the term infant. Diets such as human milk or premature infant formulas are well tolerated. For nurses, a basic understanding of these mechanisms of absorption is essential so that the rationale for various dietary adjustments can be understood.

VITAMINS, MACROMINERALS, AND TRACE MINERALS

Infants received most of their fat-soluble vitamin stores during the last trimester of pregnancy. Premature infants will have lower vitamin A, D, E, and K stores than the term infant. Premature infants do not absorb fat-soluble vitamins well because of their poor ability to digest and absorb fat (Leaf & Lansdowne, 2014). Premature infants have decreased bile salts and pancreatic lipase concentrations, both of which are needed for fat and fat-soluble vitamins to be absorbed. Premature infants have increased vitamin needs due to limited vitamin stores, increased demand for growth, and limited absorptive capabilities.

Water-soluble vitamins—B complex and vitamin C—are less likely to create deficiency states owing to their relative availability and method of absorption in infants. Information on water-soluble vitamin needs are limited for the premature infant, and there is much to be learned (Leaf & Lansdowne, 2014).

The absorption of sodium, potassium, chloride, and bicarbonate across the intestinal mucosa in the infant appears to differ from that in the adult. Under normal circumstances, this difference appears to be of no consequence. In unusual circumstances, such as diarrhea, the increased intestinal permeability may lead to large intestinal losses of these electrolytes as well as water. This causes the infant to develop dehydration and electrolyte imbalance more rapidly than later in life. Basic requirements also vary in the infant because renal absorption and excretion of these minerals are not well regulated owing to organ immaturity, which is accentuated in the premature infant.

Calcium absorption occurs by active transport and passive diffusion (Namgung & Tsang, 2017). Active transport depends on vitamin D. Passive diffusion of calcium may be enhanced by the presence of bile salts and lactose. Bile salts and lactose increase intestinal cell permeability.

Zinc that is ingested, as well as that which is resecreted from pancreatic and biliary secretions, is absorbed in the small bowel (AAP Committee on Nutrition, 2014d). Absorption varies based on the bioavailability of the source and the presence of other minerals in the diet such as iron and copper, which are known to interfere with absorption (Domellof, 2014).

GASTROINTESTINAL FUNCTION OF THE PREMATURE INFANT

Research on the developing fetus has determined that much of the gastrointestinal tract begins to function early in fetal life. Anatomically, the foregut and hindgut are present as early as 4 weeks' gestation, with the intestinal villi appearing at 8 weeks (Mahe, Helmrath, & Shroyer, 2017; Parry, 2017). It is clear, however, that even in the full-term infant, the gastrointestinal tract is inefficient in its ability to propel, absorb, and utilize nutrients and maintain homeostasis during stress.

Developmentally, the issues of the premature infant begin with the inability to suck, swallow, and breathe in a coordinated fashion. This problem places a heavy burden on the caregiver to provide adequate nutrient intake via all artificial methods. Suck, swallow, and breath coordination matures around 32 to 34 weeks' gestation. There are many additional reasons why this coordination can be delayed. For example, it is common to observe late coordination in infants who have cardiorespiratory disease and who are physiologically unstable. Another large group of infants who cannot regulate their own intake is those that remain on assisted ventilation. The sequence of the infant suck, swallow, and breathe pattern has been described as mature when the suck/swallow/respiration has a 1:1:1 to 2:2:2 pattern (Amaizu, Shulman, Schanler, & Lau, 2008). This sequence not only presumes maturity of the infant but also depends on physiologic stability. Nonnutritive sucking has obvious differences from nutritive sucking that make it only one of several indicators of feeding readiness.

The second physiologic issue of the premature is the absence or weakness of the gag and cough reflexes. This challenge increases the risks to premature infants when gastric enteral feedings are used. The risk of aspiration must be considered when the stomach is used for feeding. The assessment for presence of the gag reflex

is easy to do by direct observation while passing a feeding tube. It is nearly impossible to assess the adequacy of the gag reflex in the prevention of aspiration if vomiting or reflux occurs. **Quality and Safety: The risk of aspiration should be considered in all premature infants when started on enteral feeding.** In addition, if the infant actually vomits owing to this challenge, chronic loss of nutrients becomes problematic. Reflux has frequently been linked as a cause of apnea. New research suggests that often they occur together, but it is the apnea that leads to the gastric reflux (Martin, 2017). During an apnea episode, the respiratory neural output is decreased, accompanied by relaxation of the lower esophageal tone, and results in gastroesophageal reflux. On rare occasions, reflux can result in apnea.

The third challenge is the relative relaxation of the lower esophageal sphincter. The purpose of this sphincter is to allow food to pass into the stomach. Inappropriate relaxation may lead to reflux of food back into the esophagus (Margolis & Picoraro, 2017). Inadequate sphincter function is an additional risk factor for all premature infants when orally fed.

Delayed gastric emptying is the fourth physiologic challenge in premature infants. Gastric emptying is relatively delayed in infants. This process is delayed in disease states, and nurses find that milk feedings do not predictably empty in preterm infants or sick term infants. This challenge may be the single limiting factor when the preterm infant is placed on enteral feeds in that little can be done toward feeding progression until stomach emptying occurs. If the stomach emptying remains a limiting factor, it can be bypassed with transpyloric feedings.

Intestinal dysmotility is the fifth major challenge in the premature infant. Clinicians can observe improvement around 30 to 33 weeks' gestation and maturity of motility by 36 weeks' gestation (Margolis & Picoraro, 2017). If there are central nervous system abnormalities, then motility can be adversely affected. If intestinal motility is the limiting factor in the progression of enteral feedings, it should be identified as such before multiple formula changes are made. It is always essential to identify the specific challenge as the causative factor when addressing a plan for the delivery of enteral nutrients.

Incompetence of the ileocecal valve, the sixth challenge, is not plainly assessed by the clinician. This valve acts as a barrier between small and large bowel contents, thus separating bacterial flora as well as regulating the time for the small bowel to absorb nutrients before its contents are delivered to the colon for water absorption. When reflux through this valve occurs, the small bowel is colonized with bacteria. With the presence of undigested nutrients in the small bowel and bacteria proliferation, hydrogen gas is produced. This mechanism is part of one sequence of events hypothesized to lead to NEC (Wilson-Costello, Kliegman, & Fanaroff, 2013).

The seventh and last challenge is the passage of the first meconium stool. Term infants should pass a stool within 48 hours of life (Clark, 1977). Many premature infants will pass their first stool within 48 hours of life, but some premature infants can take up to greater than 1 week of age without problems (Verma & Dhanireddy, 1993). Term infants who have not stooled by 48 hours will need to be monitored and may need to be assessed for gastrointestinal obstruction.

Summary

The premature infant has many developmental and mechanical challenges that make the use of the gastrointestinal tract difficult or impossible. The tract matures with postnatal age and physiologic stability and needs to be reassessed regularly. Feeding assessment needs to be monitored to make changes in feedings as indicated.

PARENTERAL NUTRITION

Indications

PN describes a form of providing nutrients—food and fluid—by an intravenous route other than orally. PN is indicated for very low birth weight (VLBW) infants to supplement the advancement of enteral feedings; infants with congenital abdominal or cardiac anomalies that preclude enteral nutrition; and infants that develop the gastrointestinal illnesses, NEC, short bowel syndrome, or intractable diarrhea requiring bowel rest or limitation of feedings. PN may begin the first day of life to provide hydration, glucose homeostasis, positive nitrogen balance, and normal blood calcium levels. Nutrient concentrations will be advanced as tolerated.

Infants are started on PN on the first day of life when slow feeding advancement is anticipated. Starter PN may be used that contains a set concentration of glucose, protein, and perhaps calcium. The starter PN is available 24/7 and can be infused shortly after birth to infants to promote hydration, glucose homeostasis, and nitrogen balance. Early initiation of PN for the VLBW infant improves nitrogen balance, glucose tolerance, and growth (Poindexter, Langer, Dusick, & Ehrenkranz, 2006; Thureen, Melara, Fennessey, & Hay, 2003; Valentine et al., 2009). Intravenous lipids may be provided on day 1 to provide essential fatty acids and promote nitrogen balance (Vlaardingerbroek et al., 2013). **Quality and Safety: Electrolytes are not indicated on day 1 of age.** Vitamins may not be added to the standard starter PN solutions, as they decrease the shelf life. PN can then be advanced as described in the following sections. Tables 20.1 and 20.2 provide the guidelines for PN. Table 20.3 provides parenteral calculations.

Energy

Energy intakes of 30 to 50 kcal/kg are adequate for nitrogen balance during the first days of life (Denne & Poindexter, 2007). Energy intakes of 90 to 100 kcal/kg are the goal for growth with PN. For enteral feedings, 105 to 130 kcal/kg/day will meet the needs of most premature infants (AAP Committee on Nutrition, 2014c).

Glucose

Glucose homeostasis is an issue for premature infants, and blood levels should be monitored as parenteral glucose loads are advanced to ensure tolerance. Premature infants are at risk for hyperglycemia for many reasons including an excessive glucose load is provided, gluconeogenesis continues in the presence of elevated blood glucose levels, insulin production is decreased, insulin resistance exists, stress, or the development of sepsis (Schanler & Anderson, 2008).

Neonates usually produce glucose at the rate of 3 to 5 mg/kg/minute for the term infant and up to 8 to 9 mg/kg/minute in the ELBW infant (Poindexter & Ehrenkranz, 2015). Glucose tolerance is impaired in the VLBW infant, and starting glucose at less than 6 mg/kg/minute is recommended (AAP Committee on Nutrition, 2014c). Often 4.5 to 6 mg/kg/minute is provided to the premature infant and advanced slowly to a goal of 11 to 12 mg/kg/minute to meet energy needs for growth (AAP Committee on Nutrition, 2014c). Glucose can be advanced by 1 to 2 mg/kg/minute (Carlson & Kavars, 2016). The addition of parenteral protein enhances insulin release and the tolerance of the glucose load (Thureen et al., 2003). By monitoring blood glucose loads, slowly advancing glucose loads, and providing parenteral protein, the need for additional insulin may be avoided. Insulin will decrease hyperglycemia,

TABLE 20.1

GROWING PREMATURE INFANTS—PARENTERAL GUIDELINES: ENERGY, PROTEIN, MINERALS

Nutrient	Unit (kg/day, Except As Noted)
Energy, kcal	90–100
Glucose, mg/kg/minute	11–12
Carbohydrate, g	16–17
Protein, g	2.7–4
Fat, g	3
Calcium, mg	60–80
Phosphorus, mg	39–67
Magnesium, mg	4.3–7.2
Sodium, mEq	2–4
Potassium, mEq	1.5–2
Chloride, mEq	2–4
Zinc, mcg	400
Copper, mcg	20
Selenium, mcg	2
Chromium, mcg	0.0006
Manganese, mcg	1

Sources: Data from American Academy of Pediatrics Committee on Nutrition. (2014c). Nutritional needs of the preterm infants. In R. E. Kleinman & F. R. Greer (Eds.), *Pediatric nutrition handbook* (7th ed., pp. 83–121). Elk Grove Village, IL: Author; Vanek, V. W. (2015). Review of trace mineral requirements for preterm infants: What are the current recommendations for clinical practice? *Nutrition in Clinical Practice, 30*, 720–721. doi:10.1177/0884533614563353; Vanek, V. W., Borum, P., Buchman, A., Fessler, T. A., Howard, L., Jeejeebhoy, K., ... American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Board of Directors. (2012). A.S.P.E.N. Position paper: Recommendations for changes in commercially available parenteral multivitamin and multi-trace element products. *Nutrition in Clinical Practice,* 27, 440–491. doi:10.1177/0884533612446706

but it does increase the incidence of hypoglycemia (Alsweiler, Harding, & Bloomfield, 2012). Increased weight gain and increased head circumference growth with decreased linear growth has been reported, which may reflect greater adipose deposition (Alsweiler et al., 2012). Serum glucose levels above 150 mg/dL are defined as hyperglycemia for premature infants (Poindexter & Ehrenkranz, 2015). Decreasing the glucose load is the first step in preventing increases in blood glucose levels. Insulin use is reserved

TABLE 20.2

PEDIATRIC MULTIVITAMIN BY DOSAGE FOR INFANTS

Vitamin	2 mL/kg Infants <2.5 kg	5 mL/day Infants ≥2.5 kg
Vitamin A, IU	920	2,300
Vitamin E, IU	2.8	7
Vitamin K, mcg	80	200
Vitamin D, IU	160	400
Vitamin C, mg	32	80
Thiamin, mg	0.48	1.2
Riboflavin, mg	0.56	1.4
Niacin, mg	6.8	17
Vitamin B_6, mg	0.4	1
Folate, mcg	56	140
Vitamin B_{12}, mcg	0.4	1
Biotin, mcg	8	20
Pantothenic acid, mg	2	5

Source: Data from American Academy of Pediatrics Committee on Nutrition. (2014c). Nutritional needs of preterm infants. In R. E. Kleinman & F. R. Greer (Eds.), *Pediatric nutrition handbook* (7th ed., pp. 83–121). Elk Grove Village, IL: Author.

TABLE 20.3

CALCULATIONS FOR PARENTERAL NUTRITION

Nutrient	Calculations
Dextrose	3.4 kcal/g
Protein	4 kcal/g
20% Lipid	10 kcal/g (which is 9 fat kcal and 1 glycerol kcal) or 2 kcal/mL (1 fat g/5 mL)
GIR mg/kg/min	([mL/kg/day] × [grams glucose/100 mL] × [1,000 mg/g])/1,440 minute/day For example, infant receiving 130 mL/kg/day of 12.5% dextrose ([130 mL/kg/day] × [12.5 g dextrose/100 mL] × [1,000 mg/g])/1,440 GIR = 11.3 mg/kg/minute

GIR, glucose infusion rate.

for infants with persistent blood glucose levels over 200 mg/dL (Poindexter & Ehrenkranz, 2015). The precise blood glucose level used to indicate insulin therapy has not been defined. Tight blood glucose control is not recommended for premature infants because of the increased incidence of hypoglycemia and mortality (Alsweiler et al., 2012; Beardsall et al., 2008).

Premature infants are at risk for hypoglycemia due to poor glycogen stores, impaired gluconeogenesis, increased glucose need with acute illness (sepsis, respiratory distress), maternal therapy with beta-blockers, and hyperinsulinemia commonly seen with infants of diabetic mothers (Burris, 2017). **Emergency Alert: Hypoglycemia will occur when inadequate glucose is provided, glucose is not delivered due to intravenous line infiltration, PN has been rapidly discontinued, or insulin has been administered.**

Protein

Protein may be started at 2 to 3 g/kg/day and results in normal plasma amino acid levels, increased nitrogen balance, and increased protein anabolism (AAP Committee on Nutrition, 2014c; Denne & Poindexter, 2007; Thureen et al., 2003). Early protein intake of 3 g/kg/day is associated with better gain in weight, length, and head circumference at 36 weeks' postmenstrual age, and decreased incidence of head circumference less than the 10th percentile at 22 months corrected age (Poindexter et al., 2006).

Protein is advanced to 3.5 to 4 g/kg/day (AAP Committee on Nutrition, 2014c; van Goudoever, Vlaardingerbroek, van den Akker, de Groof, & van der Schoor, 2014). During the first week of life, blood urea nitrogen (BUN) does not consistently correlate to parenteral protein intake and should not be used to limit protein intake unless renal dysfunction is demonstrated by decreased urine output and elevated serum creatinine (Blanco, Falck, Green, Cornell, & Gong, 2008; Radmacher, Lewis, & Adamkin, 2009; Ridout, Melara, Rottinghaus, & Thureen, 2005). BUN level can reflect hydration status, excessive protein intake, inadequate protein or energy intake, illness, renal function, and hepatic synthesis (Radmacher et al., 2009).

Parenteral protein is provided as amino acids, and the use of the pediatric solutions is recommended. Three pediatric solutions are available in the United States: Aminosyn-PF (ICU-Medical), Premasol (Baxter), and TrophAmine (B. Braun; Poindexter & Ehrenkranz, 2015). These solutions provide a blend of amino acids to produce blood amino acid levels similar to those found with breastfed, term infants, or cord blood levels found with premature infants (Poindexter & Ehrenkranz, 2015). The premature infant's ability to synthesize cysteine, tyrosine, and arginine is limited, so these should be provided in the early diet. Cysteine is not stable in solutions, so it is added as cysteine hydrochloride. The addition of cysteine improves nitrogen balance and increases the acidity of the solution, which allows greater amounts of calcium and phosphorous to be added (Soghier & Brion, 2010).

Lipids

Intravenous lipids are given to provide essential fatty acids and kilocalories. One-half to 1 g of lipids will meet the essential fatty acid requirement of linoleic acid (Poindexter & Ehrenkranz, 2015). Not providing lipids in the first week of life can result in biochemical fatty acid deficiency for premature infants with limited fat stores. Intravenous lipids may be started at 1 to 2 g/kg on day 1 of life and advanced to 3 g/kg/day (AAP Committee on Nutrition, 2014c). Infants who have decreased serum levels of lipoprotein lipase or suffer from metabolic stress may not clear lipids well. Infants most at risk include those who are small for gestational age, suffer from intrauterine growth restriction, are early gestational age, extremely low birth weight, have sepsis, or have received steroids (AAP Committee on Nutrition, 2014c; Choi et al., 2015; Shulman & Phillips, 2003). To promote clearance of the triglycerides in lipids, the lipids should be provided over 24 hours, and 20% emulsions should be given (Poindexter & Ehrenkranz, 2015). The phospholipid emulsifier decreases the clearance of fatty acids, and the concentration of emulsifier is the same in the 10% and 20% emulsions. By using 20% emulsion, less volume and less phospholipid will be given per gram of lipid (5 vs. 10 mL) (AAP Committee on Nutrition, 2014c; Lapillonne, 2014). Serum triglycerides may be monitored, but acceptable levels have not been determined (Neu, 2009). A level less than 200 mg/dL has been suggested (AAP Committee on Nutrition, 2014c).

In the United States, soybean oil emulsions (Intralipid) are available. The soy oil provides the essential fatty acids of linoleic acid (omega-6 fatty acid) and linolenic acid (omega-3 fatty acid). A fish oil emulsion (Omegaven) from Europe has been only available when approval for compassionate use was obtained from the United States Food and Drug Administration (FDA) to treat parenteral nutrition associated liver disease (PNALD; Premkumar, Carter, Hawthorne, King, & Abrams, 2014). As of July 27, 2018, the FDA (n.d.) has approved Omegaven as a new drug to treat pediatric patients with Parenteral Nutrition Associated Cholestasis. Fish oil contains the omega-3 fatty acids, docosahexaenoic acid (DHA), and eicosapentaenoic acid and vitamin E that have anti-inflammatory and antioxidant properties, which may aid in the treatment of PNALD (Hojsak et al., 2016). Fish oil does not contain the phytosterols that are contained in soy oil and have been linked to the development of PNALD (Hojsak et al., 2016). Smoflipid (soy oil, MCTs, olive oil, and fish oil) blend is approved in the United States for adults, and it is used off label for the neonate (Premkumar & Calkins, 2018). Results of studies with the use of Smoflipid for neonates have been mixed with regard to the prevention and treatment of PNALD (Hojsak et al., 2016). Investigations are needed with Smoflipid to demonstrate growth and development for the premature infant (Premkumar & Calkins, 2018).

Carnitine

Carnitine facilitates the transport of long-chain fatty acids into the mitochondria for oxidation. Premature infants have limited carnitine stores and a decreased ability to synthesize carnitine (Clark, Chace, & Spitzer, 2017; Hay, 2008). Human milk and infant formula provide sources of carnitine, while parenteral solutions do not contain carnitine unless added. A dosage of 10 mg/kg/day may be provided for infants receiving only PN for greater than 2 to 3 weeks (AAP Committee on Nutrition, 2014c; Hay et al., 2014).

Fluid and Electrolytes

Premature infants have high and variable fluid needs based on birth weight, gestational age, clinical condition, and the environment in which the infant is nursed (Dell, 2015). **Quality and Safety: Constant monitoring and assessment are indicated to promote normal hydration status.** Monitoring includes body weight, fluid intake, urine output, stool output and other fluid losses, and serum electrolytes (Dell, 2015). A weight loss up to 15% is common in the first week of life (Dell, 2015).

Quality and Safety: Sodium is not added in the first few days of life to allow for the diuresis of the extracellular fluid, but intravenous saline infusions or flushes may be indicated. These sources of sodium must be accounted for when prescribing PN sodium. The usual sodium requirement is 2 to 4 mEq/kg/day. Potassium is not needed on the first day of life, but is added as renal function is established and serum potassium levels become normal. A potassium intake of 2 to 3 mEq/kg/day will usually

meet the needs of the infants (Poindexter & Ehrenkranz, 2015). Chloride may be provided with sodium and potassium. Acetate is indicated when acidosis occurs (Poindexter & Ehrenkranz, 2015). All serum electrolytes require monitoring to ensure normal serum levels.

Calcium, Phosphorus, and Magnesium

Calcium, phosphorus, and magnesium are needed for metabolic management and bone mineralization. Calcium and phosphorus should be provided at a 1 to 1.3/1 molar ratio of calcium to phosphorus to promote normal blood levels and bone mineralization (Carlson & Kavars, 2016). Calcium and phosphorus need to be provided together instead of in alternate-day administrations to avoid urinary mineral wasting or abnormal blood calcium and phosphorus levels (Carlson & Kavars, 2016). Phosphorus is often not included in starter PN solutions. Phosphorus needs to be added to the next order of PN to avoid hypercalcemia and hypophosphatemia (Hair, Chetta, Bruno, Hawthorne, & Abrams, 2016).

Vitamins

Pediatric multivitamin injections are available but are not designed for the premature infant (AAP Committee on Nutrition, 2014c). The dosage schedule is based on the infant's weight and is shown in Table 20.2. At these intakes, adequate amounts of vitamins E and K are provided, low amounts of vitamins A and D are given, and many B vitamins are greater than recommendations (AAP Committee on Nutrition, 2014c). Parenteral vitamins are not available as single vitamins.

Trace Minerals

Trace mineral guidelines are shown in Table 20.1. Trace minerals are available as multimineral packets or as separate minerals. Extra zinc is indicated for infants with intestinal losses and monitoring blood zinc levels may be helpful (Domellof, 2014; Schanler & Anderson, 2008; Shulman, 1989). When cholestasis is present, copper and manganese intakes are decreased due to elimination of these trace minerals in the bile. With restricted copper intake, blood copper levels may need to be monitored to detect copper deficiency (Marquardt, Done, Sandrock, Berdon, & Feldman, 2012). Selenium and chromium intakes are limited with impaired renal function (AAP Committee on Nutrition, 2014c).

ENTERAL NUTRITION

Premature infants have increased nutrient needs to support fetal growth. Table 20.4 provides enteral nutrient guidelines. Enteral feedings are always the goal for the nourishment of premature infants. The infant should be evaluated daily for starting feeds, feed advancement, milk fortification, or vitamin and mineral supplements.

Oral Care With Colostrum

Colostrum from the infant's own mother can be provided on the first day of life to support the infant's oral microbiota development (Gephart & Weller, 2014; Sohn, Kalanetra, Mills, & Underwood, 2016). Colostrum can be provided by syringe or swab into the buccal pouch of the oral cavity. Research is needed to establish dose frequency and duration of oral care (Gephart & Weller, 2014).

Human Milk

The milk of choice for all infants is human milk, and pasteurized donor human milk is recommended as a supplement to the infant's own mother's milk for all premature infants (Eidelman et al., 2012). The human milk diet for the premature infant results in a decreased incidence of mortality, sepsis, NEC, retinopathy of prematurity, and bronchopulmonary dysplasia, improved neurodevelopment, and a quicker time to full enteral feedings with less days of PN needed (Abrams, Schanler, Lee, Rechtman, & the Prolacta Study Group, 2014; Hair, Peluso, et al., 2016; Meinzen-Derr et al., 2009; Schanler, Shulman, & Lau, 1999; Sisk, Lovelady, Dillard, Gruber, & O'Shea, 2007; Sullivan et al., 2010; Vohr et al., 2007).

Pasteurized donor milk needs to be obtained from one of the donor human milk banks or commercial banks to ensure safety

TABLE 20.4

ENTERAL NUTRIENT GUIDELINES FOR GROWING PREMATURE INFANTS (U/KG/DAY)

Nutrient	Amount	Nutrient	Amount
Energy, kcal	105–130	Selenium, mcg	5–10
Protein, g	3.5–4.5	Iodine, mcg	10–55
Carbohydrate, g	10–14	Vitamin A, IU	1,332–3,663
Fat, g	5–7	Vitamin D, IU	200–400[a]
Calcium, mg	150–220	Vitamin E, IU	2.2–11
Phosphorus, mg	75–140	Vitamin K, mcg	4.4–28
Magnesium, mg	7.9–15	Vitamin C, mg	20–55
Sodium, mEq	3–5	Thiamin, mcg	140–300
Potassium, mEq	2–5	Riboflavin, mcg	200–400
Chloride, mEq	3–5	Niacin, mg	1.5–5
Iron, mg	2–4	Vitamin B_6, mcg	50–300
Zinc, mcg	1,000–3,000	Folate, mcg	35–100
Copper, mcg	120–150	Vitamin B_{12}, mcg	0.1–0.8
Chromium, mcg	0.03–2.25	Biotin, mcg	1.7–16.5
Manganese, mcg	1–15	Pantothenic acid, mg	0.5–2.1

[a] Vitamin D intake is per day.

Sources: Data from American Academy of Pediatrics Committee on Nutrition. (2014c). Nutritional needs of preterm infants. In R. E. Kleinman & F. R. Greer (Eds.), *Pediatric nutrition handbook* (7th ed., pp. 83–121). Elk Grove Village, IL: Author; Koletzko, B., Poindexter, B., & Uauy, R. (2014). Recommended nutrient intake levels for stable, fully enterally fed very low birth weight infants. In B. Koletzko, B. Poindexter, & R. Uauy (Eds.), *Nutritional care of preterm infants scientific basis and practical guidelines* (pp. 297–299). Basel, Switzerland: Karger.

of the product. Donors are screened for infections, medications, drugs, or high-risk activities by history and blood tests. Mothers who would like to donate milk should be referred to one of the banks for proper screening. The Human Milk Banking Association of North America (www.hmbana.org) is a volunteer association that nonprofit Human Milk Banks may be a member of and whose members are required to meet the standards for human milk banking guidelines, set by the association guidelines (AAP Committee on Nutrition, 2014c).

Fortification by a multinutrient fortifier is indicated for VLBW infants to meet their increased nutrient demands. Bovine milk fortifiers are available as powder packets or liquid vials. These fortifiers contain carbohydrate, fat, protein, vitamins, and minerals. Iron supplements will be needed if a low-iron fortifier is used. The bovine fortifiers have been added at 100 mL/kg of human milk intake (Kim et al., 2015; Moya, Sisk, Walsh, & Berseth, 2012). Donor human milk fortifiers contain human milk with concentrated protein and additives of calcium, phosphorus, and zinc. Multivitamins and iron supplements are needed with this fortifier. Donor human milk fortifiers have been added at 40, 60, 100, or 120 mL/kg of human milk intake (Hair, Peluso, et al., 2016; Sullivan et al., 2010). Table 20.5 compares human milks with the fortifiers fed at a standard volume of 150 mL/kg and at the usual milk kilocalorie concentrations.

TABLE 20.5

SELECTIVE NUTRIENT COMPARISON OF HUMAN MILK WITH FORTIFICATION—150 ML/KG

Nutrient	AAP (2014c) and Koletzko, Poindexter, & Uauy (2014) (/kg)	Human Milk (20 kcal/oz)	Human Milk + Liquid Bovine Milk Fortifier (24 kcal/oz)	Human Milk + Donor Milk Fortifier (24 kcal/oz)
Energy, kcal	105–130	101	120	120
Protein, g	3.5–4.5	1.4	3.6–3.9	2.9
Calcium, mg	150–220	35	174–179	182
Iron, mg	2–4	0.1	0.6–2.3	0.2
Zinc, mg	1–3	0.3	1.5–1.8	1.3
Vitamin D, IU	200–400/day	1.5	176–236	40

Note: Representing usual volume intakes and milk concentrations without vitamin and mineral supplementation.
Sources: Data from Abbott. (2018, June 28). Abbott Nutrition product guide. Retrieved from https://abbottnutrition.com; American Academy of Pediatrics Committee on Nutrition. (2014a). Appendix R: Representative values for constituents of human milk. In R. E. Kleinman & F. R. Greer (Eds.), *Pediatric nutrition handbook* (7th ed., pp. 1431–1432)., Elk Grove Village, IL: Author; Mead Johnson Nutrition. (2012). *Professional center, product information.* Retrieved from https://www.meadjohnson.com/professional/productinformation; Prolacta Bioscience. (2018). *Products. Prolact+ H*$^{2MF®}$ *nutrition information.* Retrieved from https://www.prolacta.com

The donor milk fortifier is available as 24, 26, 28, and 30 kcal/oz supplements. The 26 kcal/oz fortification is often used to provide more protein and energy to support growth. The 28 and 30 kcal/oz supplements are helpful with infants who are fluid restricted. A pasteurized human milk cream is available to increase the mother's or donor human milk to 20 kcal/oz. This supplement has led to improved weight gain and growth in length (Hair et al., 2014).

Infant Formulas

Premature infant formulas are more nutrient dense than standard infant formulas and contain nutrients in a more easily digested form. Table 20.5 shows a selected nutrient comparison. Premature infant formulas come as 20, 24, and 30 kcal/oz milks. The 20 and 24 kcal/oz milks will meet the needs of most premature infants. The 30 kcal/oz milk is indicated for infants who are fluid restricted. The 30 kcal/oz milk can be mixed with 24 kcal/oz milk at different proportions to make milks greater than 24 kcal/oz. The 24 kcal/oz premature formulas are available as regular and high protein. See Table 20.6 for comparison of formulas fed at a standard volume of 150 mL/kg.

Postdischarge milks are designed for the premature infant at discharge. The nutrient composition is in between the composition of standard and premature infant formulas. Studies on these formulas have been on infants less than 1,800 g birth weight (Carver et al., 2001; Koo & Hockman, 2006; Lucas et al., 2001). Studies have shown both improved growth and poorer growth for premature infants fed postdischarge formula as compared

TABLE 20.6

SELECTIVE NUTRIENT COMPARISON OF INFANT FORMULAS—150 ML/KG

Nutrient	AAP (2014c) and Koletzko et al. (2014) (/kg)	Standard (Term) (20 kcal/oz)	Premature High Protein (24 kcal/oz)	Postdischarge (22 kcal/oz)
Energy, kcal	105–130	101	120	110
Protein, g	3.5–4.5	2.0–2.2	4.0–4.4	3.1–3.2
Calcium, mg	150–220	67–80	201–219	117–134
Iron, mg	2–4	1.5–1.8	2.2	2.0
Zinc, mg	1–3	0.8–1.0	1.8	1.1–1.3
Vitamin D, IU	200–400/day	60–76	182–360	84–112

Note: Representing usual volume intakes and milk concentrations without vitamin and mineral supplementation.
Sources: Data taken from Abbott. (2018, June 28). Abbott Nutrition product guide. Retrieved from https://www.abbottnutrition.com; Gerber Good Start Formulas. (2018, June 28). Retrieved from https://www.gerbergoodstart.com; Mead Johnson Nutrition. (2012). Professional center, product information. Retrieved from https://www.meadjohnson.com/professional/productinformation;

to the term formulas. There have been reports of better growth for infants fed these formulas for 6 to 9 months (Carver et al., 2001; Lucas et al., 2001). Premature infants who are formula fed should be evaluated for these formulas at discharge (AAP Committee on Nutrition, 2014c). A recommendation has been made that the infant's weight for length be consistent at the 25th percentile to discontinue the discharge milks (AAP Committee on Nutrition, 2014b). Premature infants receiving this formula will not require additional vitamins (AAP Committee on Nutrition, 2014c). Infants will receive 2 mg/kg/day of iron on these formulas at normal volume intake. The iron guideline is 2 to 4 mg/kg/day (AAP Committee on Nutrition, 2014c). Additional iron may be provided if needed.

Soy infant formulas are not recommended for premature infants, because they have low mineral and vitamin content (Abrams et al., 2013). The absorption and utilization of nutrients by premature infants is not documented with the currently available soy formulas (AAP Committee on Nutrition, 2014c).

Specialized infant formulas including the protein hydrolysates and free amino acid formulas are used for infants with malabsorption problems such as short gut who do not tolerate human milk. Vitamin or mineral supplementation may be needed with these formulas, as they are not designed to meet the needs of the premature infant.

Feeding Management

Enteral feedings should be considered for all infants. Trophic feedings that are small feedings to feed the gut and do not serve as a major nutrition source are frequently used for infants who are VLBW or clinically stressed. Studies have ranged from 1 to 25 mL/kg/day, and human milk is the milk of choice (AAP Committee on Nutrition, 2014c). Reported benefits of early small feedings include decreased incidence of indirect hyperbilirubinemia, cholestatic jaundice, and metabolic bone disease, increased concentrations of gastric hormones, full feedings achieved more quickly, faster maturation of intestinal motility patterns, increased lactase activity, and reduced intestinal permeability (Berseth, 1992; Dunn, Hulman, Weiner, & Kliegman, 1988; Meetze et al., 1992; Shulman et al., 1998a, 1998b). By meta-analysis, the incidence of NEC was not increased with trophic feedings (Morgan, Bombell, & McGuire, 2013). There is no standard time for the length of trophic feedings as the studies have used different lengths of time for trophic feeding, different days of life to initiate feedings, and different milks. Trophic feedings can be initiated with umbilical catheters in place (Davey, Wagner, Cox, & Kendig, 1994).

Nutritive feedings are often advanced by 10 to 35 mL/kg/day for VLBW infants (Senterre, 2014). One review compared studies that used 15 to 20 mL/kg/day versus 30 to 40 mL/kg/day feeding rate advancement (Oddie, Young, & McGuire, 2017). No difference was reported in the incidence of mortality and NEC between the slow or more rapidly fed feeding groups. The smaller volume rates resulted in longer times to achieve full enteral feeding volumes and a borderline increased incidence of sepsis was noted.

Several investigations report that the implementation of a standardized feeding guideline including the use of human milk in the neonatal intensive care unit (NICU) is associated with a decrease in the incidence of NEC (Nathan et al., 2018; Patole & de Klerk, 2005).

Feeding Method

The feeding method for the infant will depend on the infant's gestational age, weight, clinical condition, and the experience of the nursery nursing staff (AAP Committee on Nutrition, 2014c). The premature infant does not coordinate sucking, swallowing, and breathing until 32 to 34 weeks' gestation. Nasogastric and orogastric feedings are used for infants too young or ill to breastfeed or bottlefeed (AAP Committee on Nutrition, 2014c). Transpyloric feedings are used for infants with persistent gastric residuals or emesis without intestinal pathology present, but research is lacking to support this method for routine feeding of premature infants (AAP Committee on Nutrition, 2014c; Watson & McGuire, 2013). Continuous milk infusion is needed for infants fed via transpyloric feedings, as the intestine has limited compliance (Schanler & Anderson, 2008). Gastrostomy feedings are indicated for infants with congenital anomalies or neurologic impairment (Sapsford & Smith, 2016).

Continuous and bolus feedings are used with gastric feedings, and there have been numerous studies suggesting that each method is best (Premji & Chessell, 2011). One concern with continuous infusion is the reported loss of fat and calcium (Rogers, Hicks, Hamzo, Veit, & Abrams, 2010).

Feeding Assessment

Feeding assessment is indicated for premature infants because they do not tolerate feedings well and are at risk for illness. Consensus is lacking on the criteria to evaluate feeding tolerance (Schanler & Anderson, 2008). Clinical assessment may include physical examination of the abdomen, the presence or absence of bowel sounds and their quality, gastric residuals, emesis, and changes in stool (Schanler & Anderson, 2008). Gastric residuals may be due to immature intestinal motor activity, feeding intolerance, NEC, or intestinal obstruction (Anderson, 2012). Residuals are frequently noted before feedings are initiated and during trophic feedings. These residuals may be ignored if no other signs of feeding tolerance or illness are present. Residuals at 50% or greater of a bolus feeding or 1.5 times an hourly rate for continuous feedings had been suggested to evaluate the infant for intolerance/illness (Schanler et al., 1999). A residual volume of 2 to 3 mL/kg per feed has also been used (Schanler et al., 1999). Shulman, Ou, and Smith (2011) reported that the premature infant's gastric residuals do not correlate with the obtaining of full gavage feedings. A recent study suggests that the use of selective gastric residual check instead of routine checking is linked to the achievement of full enteral feedings sooner without an increased incidence of NEC (Riskin et al., 2017). The bilious residual may be due to the feeding tube moving into the intestine, bile reflux into the stomach, or intestinal obstruction (Schanler & Anderson, 2008).

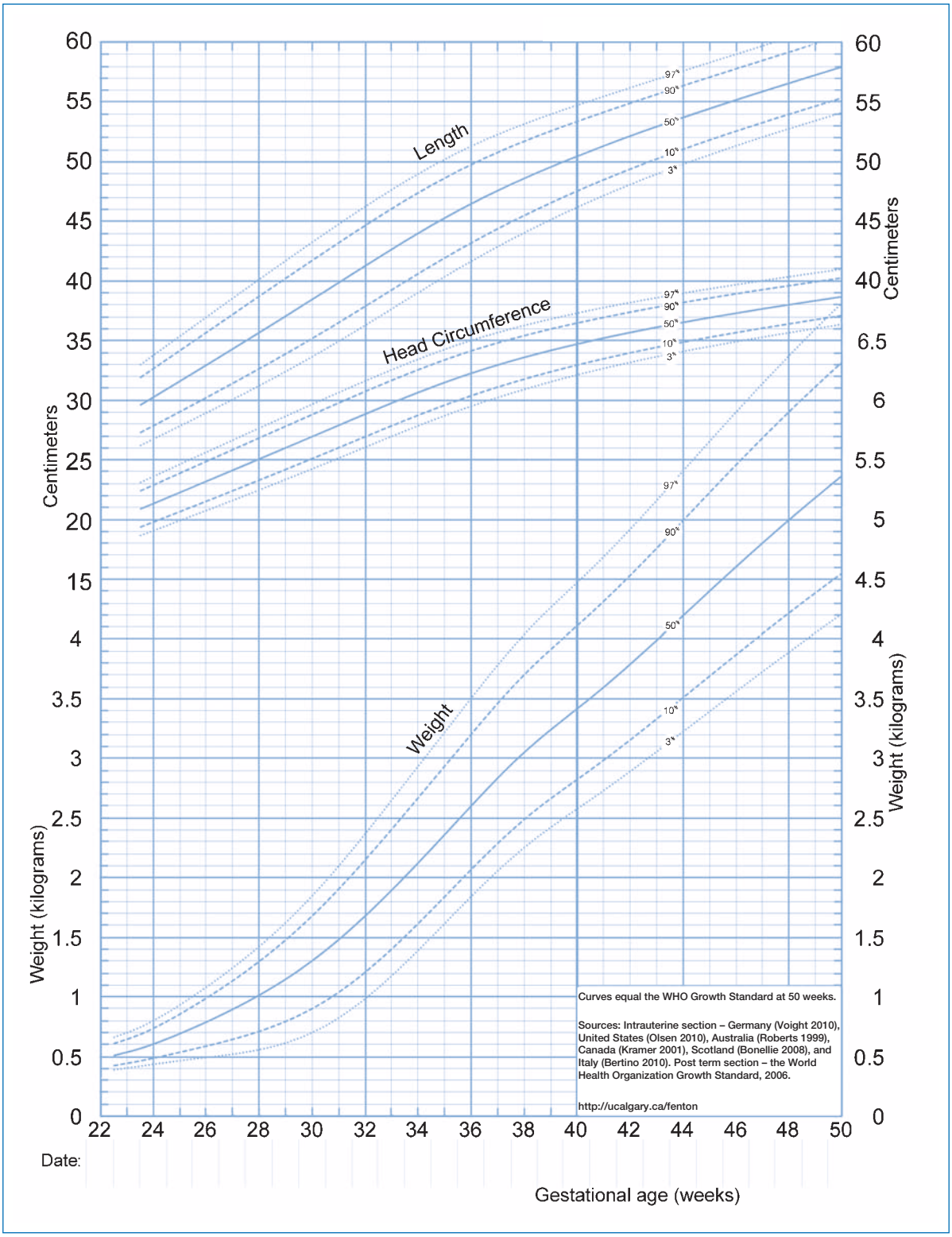
The tonicity of the abdomen should be evaluated. An increase in tonicity will occur with air swallowing, feeding intolerance, infrequent stooling, or NEC. Visual loop of bowel may indicate illness. A workup for obstruction, NEC, and sepsis may be indicated, especially if other signs of illness are present, such as an increased number of apneas and bradycardias, an increased number of desaturation events, or the presence of lethargy (Schanler & Anderson, 2008).

Blood in the residual or stool is a worry and needs to be evaluated. Etiologies include a sign of illness, feeding-tube irritation of the intestine, anal fissure, or blood swallowed during delivery (Anderson, 2012).

GROWTH AND GROWTH CHARTS

Daily weights, weekly lengths, and weekly head circumferences should be obtained, and weekly measures should be plotted on intrauterine growth curves. The intrauterine charts are developed from the birth weight, birth length, and birth head

circumferences from a large group of infants (Fenton & Kim, 2013; Olsen, Groveman, Lawson, Clark, & Zemel, 2010). Premature infants can be plotted against these charts to assess how their growth compares to the goal of fetal growth (AAP Committee on Nutrition, 2014c). The Fenton chart is a fetal infant chart that goes from 22 weeks' gestation to 50 weeks' postmenstrual age (Fenton & Kim, 2013). The fetal portion is based on infants from Germany, the United States, Italy, Australia, Scotland, and Canada and the 40 to 50 weeks is taken from the World Health Organization (WHO) growth charts. The Fenton chart is electronically available from the website (http://ucalgary.ca/fenton; Figure 20.1A and 20.1B).

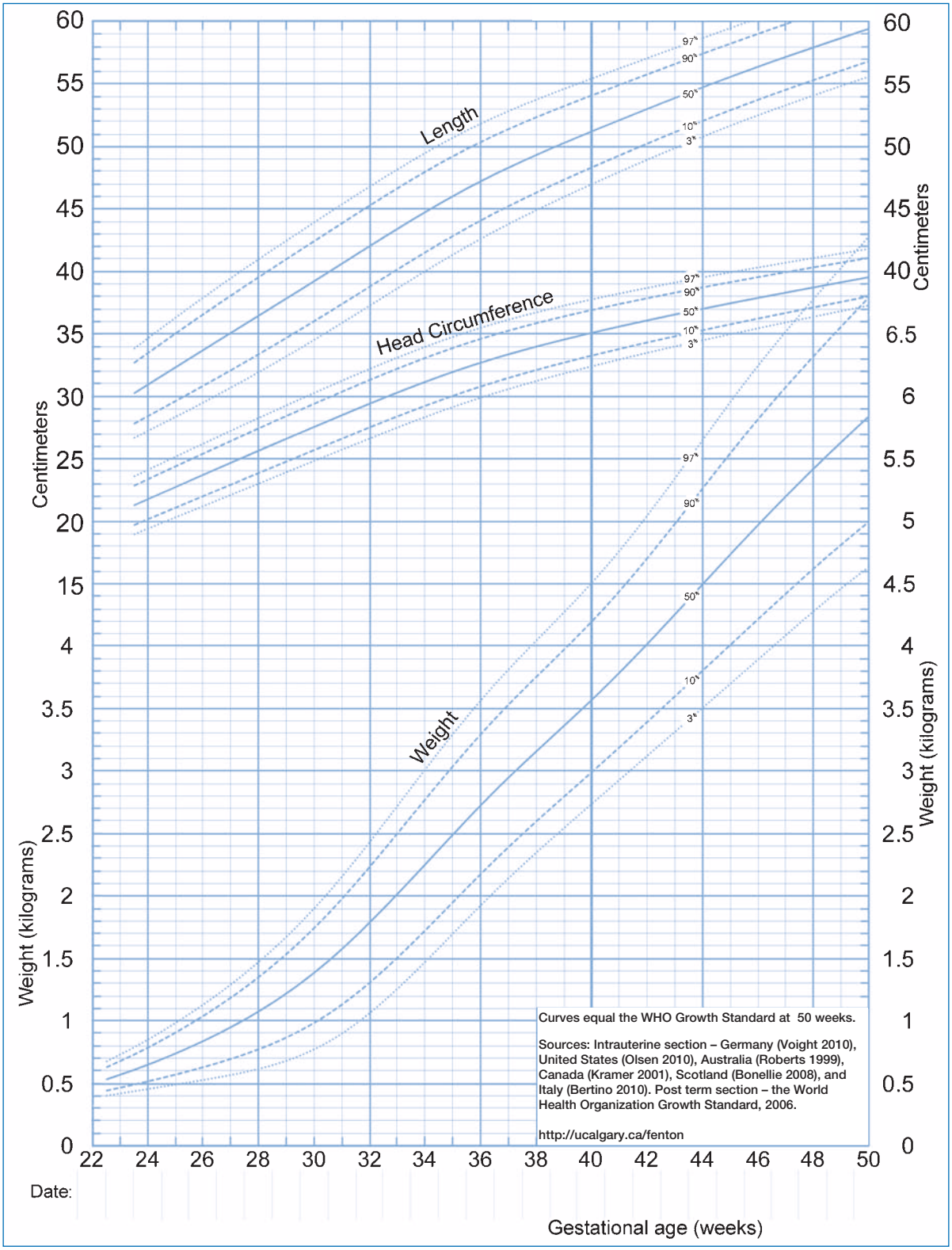


(A)

FIGURE 20.1 (A) Fenton preterm growth chart for girls. (B) Fenton preterm growth chart for boys. (*continued*)

WHO, World Health Organization.

Source: Reproduced with permission from Tanis R. Fenton, PhD. Retrieved from http://ucalgary.ca/fenton



(B)

FIGURE 20.1 (*continued*)

The Olsen chart is based on a large, racially diverse sample from the United States and goes from 23 to 41 weeks' gestation (Olsen et al., 2010). The gender-based charts include weight, length, and head circumference. These charts may be downloaded for individual patient use at the following: www.aap.org/en-us/Documents/GrowthCurves.pdf

Once the premature infant reaches 40 weeks' postmenstrual age, the WHO growth charts can be used to assess catch-up growth (Grummer-Strawn, Reinold, & Krebs, 2010). These charts are based on the growth of infants who were predominantly breastfed for the first year of life and represent ideal growth. The WHO growth charts can be downloaded from https://www.cdc.gov/growthcharts/who_charts.htm.

The INTERGROWTH-21st Project produced birth classification charts for the very preterm infants of 24 to 33 weeks' gestation and another chart from 24 to 42 weeks' gestation

TABLE 20.7

GROWTH GOALS

Weight gain	15–20 g/kg/day for infants <2 kg 20–30 g/kg/day for infants >2 kg 15–20 g/kg/day for infants 23–36 weeks' gestation
Length gain	0.7–1 cm/week
Head circumference	0.7–1 cm/week

Sources: Data from Anderson, D. M. (2012). Nutrition for premature infants. In P. Q. Samour & K. King (Eds.), *Pediatric nutrition* (4th ed., pp. 53–69). Sudbury, MA: Jones & Bartlett; Fenton, T. R., Anderson, D., Groh-Wargo, S., Hoyos, A., Ehrenkranz, R. A., & Senterre, T. (2018). An attempt to standardize the calculation of growth velocity of preterm infants—evaluation of practical bedside methods. *Journal of Pediatrics, 196*, 77–83. doi:10.1016/j.jpeds.2017.10.005

(Villar et al., 2016). Postnatal growth charts for premature infants were developed based on the growth of 201 infants born between 26 and before 37 weeks' gestation who were followed to 64 weeks' gestation (Villar et al., 2015). Infants were born in eight countries (Brazil, China, India, Italy, Kenya, Oman, United Kingdom, and the United States). Growth charts can be downloaded from https://intergrowth21.tghn.org

During the first week of life, premature infants can lose up to 15% of their birth weight, which is the loss of extracellular fluid (Dell, 2015). Goals for weekly rate of gain are given in Table 20.7. Since weights are obtained daily, a weekly rate can be calculated daily. Closely monitoring growth is important to ensure the best growth for these high-risk infants and their future development. Extremely low birth weight (ELBW) infants have demonstrated improved neurologic outcomes and growth at 18 to 22 months of corrected age when their growth rates in the nursery were greater than 18 g/kg/day for weight or 0.9 cm/week for head circumference (Ehrenkranz et al., 2006). When poor growth occurs, assessment of the etiology should be explored. Poor growth may be related to medical conditions or nutrition management. Medical issues that may contribute to poor growth include acidosis, hyponatremia, increased work of breathing, cold stress, anemia, infections, and the use of steroids (Anderson, 2012). These conditions require treatment before nutrition can be fully utilized. Issues related to nutrition are given in Box 20.1.

Biochemical Indices

Serum electrolytes, glucose, BUN, and creatinine will be monitored daily or more frequently if abnormal during the first week of life. Once stable, these serum values will be obtained once to twice a week for the infant receiving PN or diuretics, or for the infant who has an abnormal value (Anderson, 2012). While on PN, serum conjugated bilirubin and serum alanine aminotransferase (ALT, serum glutamic-pyruvic transaminase) will be drawn weekly starting at 2 weeks of PN therapy to detect PNALD. Serum phosphorus and alkaline phosphatase activity levels are drawn on infants at risk for osteopenia, which includes VLBW infants and infants with a prolonged course of PN or milk intake of formula not designed for premature infants. If alkaline phosphatase activity levels reach 800 IL/L, a radiograph of the wrist/knees (rickets survey) can be used to document metabolic bone disease of prematurity (Mitchell et al., 2009). Hematocrit and hemoglobin levels are obtained as needed (Schanler & Anderson, 2008).

Box 20.1

CONSIDERATIONS FOR POOR GROWTH—NUTRITION FACTORS

Feeding intolerance—abnormal stools, excessive residuals, or emesis

Full nutrition just achieved that meets nutrient guidelines

Nutrition Not Optimized

Parenteral nutrient concentrations not adequate

Incorrect amount of fortifier added to human milk

Incorrect calculations

Human Milk

Continuous infusions will lead to fat losses

Use of foremilk that is low in fat and kilocalories

Ordered Diet Not Received

Infant not able to consume adequate milk and is not supplemented with gavage feedings

Feedings held for tests

Volume of feedings ordered per kg has not kept up with weight gain

Nutrition Solution Not Prepared Correctly, or Incorrect Milk Feeding Provided

Intravenous fluid administration has been held to provide medication or blood

Ostomy output is excessive, so parenteral fluids will need to be increased and enteral feedings decreased to meet infant's nutrition needs

Source: Data from Anderson, D. M. (2012). Nutrition for premature infants. In P. Q. Samour & K. King (Eds.), *Pediatric nutrition* (4th ed., pp. 53–69). Sudbury, MA: Jones & Bartlett.

POSTDISCHARGE NUTRITION

Prior to discharge, the infant's nutritional status should be assessed for present growth status, feeding volume allowed and infant's actual volume intake, presence of any abnormal serum levels that require treatment, and the mother's desire to breastfeed. Depending on the infant's history regarding osteopenia, ability to nurse, and fluid allowance, the infant's feeding recommendation will be individualized. The infant should be placed on the discharge diet prior to discharge to assess growth and feeding tolerance to the plan. Parents need to demonstrate their ability to feed their infant, administer supplements, and prepare special milks if indicated.

The breastfed infant will need multivitamins and iron to provide vitamin D at 400 IU/day and iron at 2 to 4 mg/kg/day (Abrams et al., 2013; AAP Committee on Nutrition, 2014c). Infants may require formula supplementation to meet needs for growth, and two to three feeds per day may be provided to increase nutrient intake. By using bottle feedings of formula instead of formula powder added to expressed human milk, the mother can actually breastfeed her infant and possibly avoid bacterial contamination of powder infant formulas. Nutrient intake can be greater with the use of two to three bottles of discharge formula than making all the human milk 22 kcal/oz with discharge formula powder.

Mothers should be referred to lactation consultation for postdischarge support.

In a recent study, discharged premature infants were for 12 weeks fed their mothers' milk, which was fortified with bovine human milk fortifier for half of their feedings, and the other half of feedings were breastfed or expressed milk (O'Connor et al., 2008). This group of infants was compared to a group of premature infants fed their mothers' milk supplemented with iron and vitamins. At 12 weeks postdischarge, the bovine human milk fortified group was longer and had greater head circumferences. At 1 year corrected age, the infants who received the bovine fortified milk were longer, had greater head circumferences, and had greater weights (Aimone et al., 2009). No differences were noted in development at 18 months corrected age (Aimone et al., 2009).

The postdischarge formula may be used for infants who are not breastfed. Vitamin and iron supplements are generally not indicated (AAP Committee on Nutrition, 2014c).

Infants should be referred to the Special Supplemental Nutrition Program for Women, Infants and Children (WIC) and to the early children intervention programs. A medical home should provide the necessary assessment and management of the infant's nutrition needs related to growth and normal development.

SUMMARY

This chapter has reviewed the basic physiology of digestion and the importance of adequate neonatal nutrition for positive growth and development. Different routes of feeding as well as different formulas and breast milk feeding have been discussed. Neonatal nutrition is a challenge but sets the course for a lifetime of health.

CASE STUDY

■ **Identification of the Problem.** Premature infant not gaining weight

■ **Assessment: History and Physical Examination.** The premature female infant was delivered by spontaneous vaginal delivery following one course of antenatal steroids to a 30-year-old G2 P1 woman. The infant required oxygen at birth and was weaned to room air by 12 hours of age. Sepsis workup was completed for preterm delivery, and results were negative. Her Apgar scores were 6^{1}, 8^{5}. She was placed in a humidified incubator. She developed hyperbilirubinemia and was treated with phototherapy from day 2 to 5 of age.

She was born at 28 weeks' gestation with a birth weight of 900 g, length of 37 cm, and head circumference of 26.5 cm. She is classified as appropriate for gestational age, for her birth weight is between the 10th and 50th percentile. Her length and head circumference are between the 10th and 50th percentile. She is now 21 days of age and 31 weeks' postmenstrual age. She regained birth weight by 2 weeks of age and now weighs 950 g, which is below the 10th percentile. Her rate of weight gain this past week was 8 g/kg/day. Her length is 38 cm, and her head circumference is 27 cm.

She was started on PN day 1 of age at 80 mL/kg/day providing 45 kcal/kg, GIR of 5.2 mg/kg/minute of glucose, 2.4 g protein/kg, and 1 g/kg of lipid. Mom's milk was started day 2 of age at 20 mL/kg/day and provided for 3 days as trophic feedings before advancing milk by 20 mL/kg/day to a volume of 150 mL/kg/day. PN was advanced to meet guidelines and was discontinued when 120 mL/kg of human milk feedings were achieved on day 9 of age. Today's diet order is human milk fortified with bovine human milk fortifier to 24 kcal/oz at 150 mL/kg/d by a continuous infusion of 5.5 mL/hour by a nasogastric tube. Diet should provide 120 kcal/kg and 3.9 g protein/kg/day.

Physical examination is normal.

■ **Differential Diagnoses**

- Infant needs formula supplement
- Infant not receiving diet as ordered
- Infant has increased requirements
- Diet order incorrect
- Infant just achieved appropriate diet
- Infant has abnormal labs
- Infant has a low temperature
- Infant is not tolerating feedings
- Documented weight incorrect
- Inadequate intake

■ **Diagnostic Tests**

- Check incubator temperature management: baby was on manual control mode at 35°C
- Recheck diet orders: at 5.5 mL/hour the infant is only receiving 140 mL/kg/day; order placed in the computer was for 22 kcal/oz milk instead of 24 kcal/oz; infant actually receiving 102 kcal/kg and 2.5 g protein/kg/day
- Review infant's flow sheet for output: no emesis, no stool for 2 days, abdomen soft
- Review vitals: yesterday the baby's skin temperature was 35°C
- Review labs: labs from 3 days ago: serum sodium 140 mEq/dL, potassium 5 mEq/dL, chloride 108 mEq/dL, BUN 12 mg/dL, hemoglobin 11 g/dL, and hematocrit 33%
- Review daily weight: slow, steady increase of 10 g/day; no large increases or decreases; weight is probably accurate

■ **Working Diagnosis**

- Infant cold stressed
- Inadequate nutrition intake

■ **Development of Management Plan**

- Change incubator temperature management to servo control mode at 37°C
- Change feeding order to 6 mL/hour to provide 150 mL/kg
- Order 24 kcal/oz human milk with bovine human milk fortifier

Implementation and Evaluation of Effectiveness

- Feeding order changed today
- Daily weights followed closely for the next 3 to 5 days to ensure good weight gain; weight gain since change in diet is 13 g/kg/day
- Change to bolus feedings to increase nutrient delivery; weight gain is now 15 g/kg/day; length and head circumference have increased 1 cm each this past week
- Once infant demonstrated good weight gain, incubator temperature management changed back to manual control mode

■ **Outcome.** Growth can occur when infant's temperature is maintained. Human milk fortified with bovine human milk fortifier to 24 kcal/oz at 150 mL/kg given as a bolus meets infant's nutritional needs. Infant's growth is appropriate on human milk fortified to 24 kcal/oz diet at 150 mL/kg.

EVIDENCE-BASED PRACTICE BOX

Cysteine is an amino acid that is a precursor for taurine and glutathione, or cysteine may go directly into protein formation (Soghier & Brion, 2010). Cysteine may be semi-essential for the premature infant due to the infant's limited ability to synthesize cysteine from methionine (Poindexter & Ehrenkranz, 2015). Cystathionase, the enzyme responsible for cysteine synthesis, has been reported at low concentrations in the livers of premature infants, yet the extrahepatic tissue may contain adequate amounts of this enzyme. Not all studies with premature infants report limited ability to synthesize cysteine (Poindexter & Ehrenkranz, 2015). Early studies did not show a positive nitrogen balance with the addition of cysteine, which may have been related to the low level of energy provided and the lack of tyrosine in some amino acid solutions (Soghier & Brion, 2010).

A recent meta-analysis compared six studies that were randomized control trials or quasi-randomized trials (Soghier & Brion, 2010). Five studies added cysteine to cysteine-free PN and compared nitrogen balance to those infants not receiving cysteine. The sixth study added *N*-acetylcysteine (cysteine precursor) to a parenteral solution containing a little cysteine. Four of the five studies with the addition of cysteine reported a positive nitrogen balance, which was significant by meta-analysis. The *N*-acetylcysteine additive did not improve nitrogen balance. Growth was only examined by two studies that reported no gains in growth. No studies reported mortality or morbidity information. Four trials examined serum cysteine levels that were significantly elevated as compared to infants not receiving cysteine. More research is needed to explore the effects of parenteral cysteine on infant growth to include changes in weight, length, head circumference, body composition, and bone mineralization (Soghier & Brion, 2010). The addition of cysteine hydrochloride increases the acidity of the parenteral solutions and permits more calcium and phosphorus to be added without precipitation of the minerals occurring (Poindexter & Ehrenkranz, 2015; Schanler & Anderson, 2008; Soghier & Brion, 2010). The addition of the cysteine hydrochloride may result in metabolic acidosis in the infant, and acetate may be added to the parenteral solution to correct or prevent the acidosis.

References

Poindexter, B. B., & Ehrenkranz, R. A. (2015). Nutrition requirements and provision of nutritional support in the premature neonate. In R. J. Martin, A. A. Fanaroff, & M. C. Walsh (Eds.), *Fanaroff and Martin's neonatal-perinatal medicine: Diseases of the fetus and infant* (10th ed., pp. 592–612). Philadelphia, PA: Elsevier.

Schanler, R. J., & Anderson, D. M. (2008). Nutrition support of the low birth weight infant. In C. Duggan, J. B. Watkins, & W. A. Walker (Eds.), *Nutrition in pediatrics* (4th ed., pp. 377–394). Hamilton, ON: BC Decker.

Soghier, L. M., & Brion, L. P. (2010). Cysteine, cystine or N-acetylcysteine supplementation in parenterally fed neonates. *Cochrane Database of Systematic Reviews*, (4), CD004869. doi:10.1002/14651858.CD004869.pub2

QUALITY AND SAFETY

- Safe tube administration of parenteral nutrition, enteral nutrition, and medications is the goal. Traditionally, one connector has been available for use with all types of tubing and has allowed the accidental connection of an enteral system to an intravenous system (Litman, Smith, & Mainland, 2018). Sentinel events of severe patient injury or death have been reported (The Joint Commission, 2014).
- Globally, new standards for small bore connectors, ISO 80369, have been developed for different clinical applications that are physically incompatible with each other and should prevent the infusion of the fluid to an incorrect site. The standards were developed with The International Organization for Standardization, the Association for Advancement of Medical Instrumentation, clinicians, manufacturers, and regulators, including the U.S. Food and Drug Administration (The Joint Commission, 2014; Litman et al., 2018).
- New connectors have new problems. The ENFit® tube has a male end and the syringe has a female end, which is reverse of the previously used feeding-tube connectors. The female end syringe has more dead space, which can lead to medication overdose if not cleared properly (Guenter & Lyman, 2016). The male end or port of the feeding tube needs to be cleaned appropriately. Residual milk or medications can be a source of bacterial growth and infection (Guenter & Lyman, 2016).
- To plan transition, Global Enteral Device Supplier Association (GEDSA) is a resource. GEDSA is a nonprofit trade association (www.StayConnected.org).
- To change to new connectors, the following is needed (Guenter & Lyman, 2016; The Joint Commission, 2014):
  - Available supplies of approved connectors
  - Commitment of the facility's chief of operations
  - Education of staff on how to use connectors
  - Quality indicators in place for assessment
  - Communication established with individual device manufacturer

PARENT VOICES

Heather Tanner

Nutrition Story in the NICU: Born at 30 weeks, our son lacked the breathe, suck, swallow reflex. He needed a central line and an NG/OG tube to deliver his nutrition. Feeding very preterm babies involves the risk of NEC. It was something I had never heard of. During the course of his 10-week stay, our son had pneumatosis twice. His feeding schedule was changed, but I wasn't told why—pneumatosis. Informing parents about common conditions like ROP, NEC, PDA . . . helps us as parents understand why his treatment was changed. Later, at 6.5 months our son developed pneumatosis again. Only this time, he was at a specialty children's hospital and they recognized it right away and told us first thing. He received evidence-based treatment, including being made NPO for 7 days and the use of parenteral nutrition during gut rest. It gave us clearer answers as to how we could advocate for his nutrition while in the hospital. Parents want to be informed decision makers. Educate them and allow their participation in the course of care. Without education, they cannot advocate.

The baby had feeding issues that required rehospitalization: Our son was born at 30 weeks diagnosed with an in utero midgut volvulus. He had abdominal surgery and lost two-thirds of his small intestine. He was on parenteral nutrition for such a short time while tube feeds were steadily increased. At 4 weeks, he was reconnected and weaned slowly off tube feeding to bottle feeding. At discharge, he drank all his feeds and was sent home without any enteral feeding necessary. At that time, he had no diagnosis other than being premature. He struggled to feed at home orally until he was 6.5 months. He had lost so much intestine in the NICU, his remaining gut was not functioning properly. He was admitted to a children's specialty hospital and finally diagnosed with intestinal failure, short bowel syndrome, and failure to thrive (FTT). What he needed from the very beginning was intestinal rehabilitation. Losing intestine requires careful nutritional monitoring long term. We had no idea that he suffered with malabsorption until 6.5 months. He was so depleted, even though he was finishing full feeds. Fed does not equal nourished.

Ali Dunn

My twins were born at 28 weeks. Much too small and fragile to eat by mouth, let alone to latch and suck. So, like many preemie mommas, I started pumping. The NICU staff that were caring for my twins stressed the importance of every drop of breast milk. The lactation consultant and the sweet NICU nurses cheered over any amount of milk I was able to express. Pumping made me feel like a mother. When I had very little to give my preemies in the NICU, pumping for them gave me a sense of purpose. When I had very little control over their care and their health, I felt empowered by my ability to provide something they needed. When I felt like my body had failed in growing my babies to term, I felt it redeemed itself by producing the perfect food for them. So, even though it was hard and time-consuming, I never gave up. And 43 days after they were born, I was able to feed my babies a bottle for the first time. The encouragement of the NICU nurses was very important in being able to establish and maintain a pumping routine that continued long after my twins left the NICU.

Deborah A. Discenza

I woke up in my postpartum room, foggy from the birth the night before. As I stared at the breast pump at the foot of my bed, I told my husband that I needed to start pumping breast milk. I figured it was one way I could help my daughter in the NICU. So not knowing what we were doing, we used the pump. It was almost comical, doing a lot of things wrong. But I pumped a little bit of yellowish liquid and told my husband to go ask the nurse if this was useful or if it should be thrown out. A few minutes later, he came back with a big grin on his face. "They are rushing it down to the NICU right now," he said. "She called it 'liquid gold.'" I was excited to have done this for my daughter and worked hard over the next couple of weeks to increase my supply. At one point, I attempted breastfeeding and did not succeed assuming that Becky would not be able to do it. I kept pumping. No one talked to me, no one educated me, I did this all on my own with a few visits to the lactation consultant for advice on pumping. At one point, I noticed the team added preemie formula to my daughter's intake. I was surprised, wondering why. My husband told me that they said it was to give our daughter the extra calories. I assumed they knew best. But then, a short time later as we started down the path toward discharge, I had a nurse bully me, saying that she breastfed her kids so I should do the same with my daughter. I was stunned and felt totally attacked. I did not know what to say, or how to defend myself. I was mad. I later called the medical director and filed a complaint and said I wanted that nurse to never care for my child again. To me, upon reflection, that nurse had no idea what I had done to care for my daughter. That should have counted. That moment of bullying should have been a moment of praise for what I had done on my own and to gently educate me, without bullying, on keeping breastfeeding ongoing as I got home with my daughter. What she did was wrong and I know that now. I did an incredible job for my daughter, who, as it turned out, had a major feeding issue that lasted until she was 12 years old when we got her into feeding therapy. Never ever assume that you know what a preemie parent is going through with pumping, breastfeeding, and more if you have been in the NICU yourself.

ONLINE RESOURCES

American Academy of Pediatrics. Retrieved from http://www.aap.org

Centers for Disease Control and Prevention. (n.d.). *World Health Organization (WHO) growth curve*. Retrieved from http://www.cdc.gov/growthcharts/who_charts.htm

Fenton growth curve. Retrieved from http://www.ucalgary.ca/fenton

Human Milk Banking Association of North America. Retrieved from http://www.hmbana.org

National Center for Education in Maternal and Child Health. Retrieved from http://www.ncemch.org

Olsen Growth Curve. Retrieved from https://www.aap.org/en-us/Documents/GrowthCurves.pdf

REFERENCES

Abbott. (2018, June). *Abbott nutrition. Product guide*. Retrieved from www.abbottnutrition.com/

Abrams, S. A., Bhatia, J. J. S., Corkins, M. R., de Ferranti, S. D., Golden, N. H., & Silverstein, J. (2013). Calcium and vitamin D requirements of enterally fed preterm infants. *Pediatrics, 131*, e1676–e1683. doi:10.1542/peds.2013-0420

Abrams, S. A., Schanler, R. J., Lee, M. L., & Rechtman, D. J.; the Prolacta Study Group. (2014). Greater mortality and morbidity in extremely preterm infants fed a diet containing cow milk protein products. *Breastfeeding Medicine, 9*(6), 281–285. doi:10.1089/bfm.2014.0024

Aimone, A., Rovet, J., Ward, W., Jefferies, A., Campbell, D. M., Asztalos, E., . . . O'Connor, D. L. (2009). Growth and body composition of human milk-fed premature infants provided with extra energy and nutrients early after hospital discharge: 1-year follow-up. *Journal of Pediatric Gastroenterology and Nutrition, 49*(4), 456–466. doi:10.1097/MPG.0b013e31819bc94b

Alsweiler, J. M., Harding, J. E., & Bloomfield, F. H. (2012). Tight glycemic control with insulin in hyperglycemic preterm babies: A randomized controlled trial. *Pediatrics, 129*(4), 639–647. doi:10.1542/peds.2011–2470

Amaizu, N., Shulman, R. J., Schanler, R. J., & Lau, C. (2008). Maturation of oral feeding skills in preterm infants. *Acta Paediatrica, 97*(1), 61–67. doi:10.1111/j.1651-2227.2007.00548.x

American Academy of Pediatrics Committee on Nutrition. (2014a). Appendix R. Representative values for constituents of human milk. In R. E. Kleinman & F. R. Greer (Eds.), *Pediatric nutrition handbook* (7th ed., pp. 1431–1432). Elk Grove Village, IL: Author.

American Academy of Pediatrics Committee on Nutrition. (2014b). Failure to thrive. In R. E. Kleinman & F. R. Greer (Eds.), *Pediatric nutrition handbook* (7th ed., pp. 663–700). Elk Grove Village, IL: Author.

American Academy of Pediatrics Committee on Nutrition. (2014c). Nutritional needs of preterm infants. In R. E. Kleinman & F. R. Greer (Eds.), *Pediatric nutrition handbook* (7th ed., pp. 83–121). Elk Grove Village, IL: Author.

American Academy of Pediatrics Committee on Nutrition. (2014d). Trace elements. In R. E. Kleinman & F. R. Greer (Eds.), *Pediatric nutrition handbook* (7th ed., pp. 467–494). Elk Grove Village, IL: Author.

Anderson, D. M. (2012). Nutrition for premature infants. In P. Q. Samour & K. King (Eds.), *Pediatric nutrition* (4th ed., pp. 53–69). Sudbury, MA: Jones & Bartlett.

Beardsall, K., Vanhaesebrouck, S., Ogilvy-Stuart, A. L., Vanhole, C., Palmer, C. R., van Weissenbruch, M., . . . Dunger, D. B. (2008). Early insulin therapy in very-low-birth-weight infants. *New England Journal of Medicine, 359*, 1873–1884. doi:10.1056/NEJMoa0803725

Berseth, C. L. (1992). Effect of early feeding on maturation of the preterm infant's small intestine. *Journal of Pediatrics, 120*(6), 947–953. doi:10.1016/S0022-3476(05)81969-9

Blanco, C. L., Falck, A., Green, B. K., Cornell, J. E., & Gong, A. K. (2008). Metabolic responses to early and high protein supplementation in a randomized trial evaluating the prevention of hyperkalemia in extremely low birth weight infants. *Journal of Pediatrics, 153*(4), 535–540. doi:10.1016/j.jpeds.2008.04.059

Burris, H. H. (2017). Hypoglycemia and hyperglycemia. In E. C. Eichenwald, A. R. Hansen, C. R. Martin, & A. R. Stark (Eds.), *Cloherty and Starks' manual of neonatal care* (8th ed., pp. 312–325). Philadelphia, PA: Wolters Kluwer.

Carlson, S. J., & Kavars, A. M. (2016). Parenteral nutrition. In Pediatric Nutrition Dietetic Practice Group, S. Groh-Wargo, M. Thompson, & J. H. Cox (Eds.), *Academy of Nutrition and Dietetics pocket guide to neonatal nutrition* (2nd ed., pp. 32–75). Chicago, IL: Academy of Nutrition and Dietetics.

Carver, J. D., Wu, P. Y. K., Hall, R. T., Ziegler E. E., Sosa, R., Jacobs, J., . . . Lloyd, B. (2001). Growth of preterm infants fed nutrient-enriched or term formula after hospital discharge. *Pediatrics, 107*(4), 683–689. doi:10.1542/peds.107.4.683

Choi, Y., Bae, H., Lee, J., Cho, E., Lee, Y., Lee, H., . . . Kim, H. (2015). Analysis of risk factors for lipid intolerance of intravenous fat emulsion in very low birth weight infants. *Archives of Pharmacal Research, 38*(5), 914–920. doi:10.1007/s12272-014-0405-6

Clark, D. A. (1977). Times of first void and first stool in 500 newborns. *Pediatrics, 60*, 457–459. doi:https://pediatrics.aappublications.org/content/60/4/457

Clark, R. H., Chace, D. H., & Spitzer, A. R. (2017). Impact of L-carnitine supplementation on metabolic profiles in premature infants. *Journal of Perinatology, 37*, 566–571. doi:10.1038/jp.2016.253

Davey, A. M., Wagner, C. L., Cox, C., & Kendig, J. W. (1994). Feeding premature infants while low umbilical artery catheters are in place: A prospective, randomized trial. *Journal of Pediatrics, 124*(5, Pt. 1), 795–799. doi:10.1016/S0022-3476(05)81376-9

Dell, K. R. (2015). Fluid, electrolytes, and acid–base homeostasis. In R. J. Martin, A. A. Fanaroff, & M. C. Walsh (Eds.), *Fanaroff and Martin's neonatal-perinatal medicine: Diseases of the fetus and infant* (10th ed., pp. 613–629). Philadelphia, PA: Elsevier.

Denne, S. C., & Poindexter, B. B. (2007). Evidence supporting early nutritional support with parenteral amino acid infusion. *Seminars in Perinatology, 31*(2), 56–60. doi:10.1053/j.semperi.2007.02.225

Domellof, M. (2014). Nutritional care of premature infants: Microminerals. In B. Koletzko, B. Poindexter, & R. Uauy (Eds.), *Nutritional care of preterm infants: Scientific basis and practical guidelines* (pp. 121–139). Basel, Switzerland: Karger.

Dunn, L., Hulman, S., Weiner, J., & Kliegman, R. (1988). Beneficial effects of early hypocaloric enteral feeding on neonatal gastrointestinal function: Preliminary report of a randomized trial. *Journal of Pediatrics, 112*(4), 622–629. doi:10.1016/S0022-3476(88)80185-9

Ehrenkranz, R. A. (2010). Early nutritional support and outcomes in ELBW infants. *Early Human Development, 86*(1 Suppl.), 21–25. doi:10.1016/j.earlhumdev.2010.01.014

Ehrenkranz, R. A., Dusick, A. M., Vohr, B. R., Wright, L. L., Wrage, L. A., & Poole, W. K. (2006). Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants. *Pediatrics, 117*(4), 1253–1261. doi:10.1542/peds.2005–1368

Eidelman, A. I., Schanler, R. J., Johnston, M., Landers, S., Noble, L., Szucs, K., & Viehmann, L. (2012). Breastfeeding and the use of human milk. *Pediatrics, 129*(3), e827–e841. doi:10.1542/peds.2011-3552

Fenton, T. R., Anderson, D., Groh-Wargo, S., Hoyos, A., Ehrenkranz, R. A., & Senterre, T. (2018). An attempt to standardize the calculation of growth velocity of preterm infants—evaluation of practical bedside methods. *Journal of Pediatrics, 196*, 77–83. doi:10.1016/j.jpeds.2017.10.005

Fenton, T. R., & Kim, J. H. (2013). A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. *BMC Pediatrics, 13*, 59. doi:10.1186/1471-2431-13-59

Gephart, S. M., & Weller, M. (2014). Colostrum as oral immune therapy to promote neonatal health. *Advances in Neonatal Care, 14*(1), 44–51. doi:10.1097/ANC.0000000000000052

Gerber Good Start Formulas. (2018, June 28). Retrieved from https://www.gerber.com/gerber-good-start

Grummer-Strawn, L. M., Reinold, C., & Krebs, N. F. (2010). Use of World Health Organization and CDC growth charts for children aged

0-59 months in the U.S. *Morbidity and Mortality Weekly Report, 59*(RR-9), 1–15. Retrieved from https://www.cdc.gov/mmWr/preview/mmwrhtml/rr5909a1.htm

Guenter, P., & Lyman, B. (2016). ENFit enteral nutrition connectors: Benefits and challenges. *Nutrition in Clinical Practice, 31*(6), 769–772. doi:10.1177/0884533616673638

Hair, A. B., Blanco, C. L., Moreira, A. G., Hawthorne, K. M., Lee, M. L., Rechtman, D. J., & Abrams, S. A. (2014). Randomized trial of human milk cream as a supplement to standard fortification of an exclusive human milk-based diet in infants 750-1250 g birth weight. *Journal of Pediatrics, 165*(5), 915. doi:10.1016/j.jpeds.2014.07.005

Hair, A. B., Chetta, K. E., Bruno, A. M., Hawthorne, K. M., & Abrams, S. A. (2016). Delayed introduction of parenteral phosphorus is associated with hypercalcemia in extremely preterm infants. *Journal of Nutrition, 146*(6), 1212–1216. doi:10.3945/jn.115.228254

Hair, A. B., Peluso, A. M., Hawthorne, K. M., Perez, J., Smith, D. P., Lee, M. L., . . . Abrams S. A. (2016). Beyond necrotizing enterocolitis prevention: Improving outcomes with an exclusive human milk-based diet. *Breastfeeding Medicine, 11*(2), 70–74. doi:10.1089/bfm.2015.0134

Hay, W. W. (2008). Strategies for feeding the preterm infant. *Neonatology, 94*(4), 245–254. doi:10.1159/000151643

Hay, W. W., Brown, L. D., & Denne, S. C. (2014). Energy requirements, protein-energy metabolism and balance, and carbohydrates in preterm infants. In B. Koletzko, B. Poindexter, & R. Uauy (Eds.), *Nutritional care of preterm infants: Scientific basis and practical guidelines* (pp. 64–81). Basel, Switzerland: Karger.

Heird, W. C., Driscoll, J. M., Schullinger, J. N., Grebin, B., & Winters, R. W. (1972). Intravenous alimentation in pediatric patients. *Journal of Pediatrics, 80*(3), 351–372. doi:10.1016/S0022-3476(72)80492-X

Hojsak, I., Colomb, V., Braegger, C., Bronsky, J., Campoy, C., Domellöf, M., . . . ESPGHAN Committee on Nutrition. (2016). ESPGHAN Committee on Nutrition position paper. Intravenous lipid emulsions and risk of hepatotoxicity in infants and children: A systematic review and meta-analysis. *Journal of Pediatric Gastroenterology and Nutrition, 62*(5), 776–792. doi:10.1097/MPG.0000000000001121

The Joint Commission. (2014). *Sentinel Event Alert 53: Managing risk during transition to new ISO tubing connector standards*. Retrieved from https://www.jointcommission.org/sea_issue_53

Kim, J. H., Chan, G., Schanler, R., Groh-Wargo, S., Sharon, B., Barry, D., . . . Barrett-Reis, B. (2015). Growth and tolerance of preterm infants fed a new extensively hydrolyzed liquid human milk fortifier. *Journal of Pediatric Gastroenterology and Nutrition, 61*(6), 665–671. doi:10.1097/MPG.0000000000001010

Koletzko, B., Poindexter, B., & Uauy, R. (2014). Recommended nutrient intake levels for stable, fully enterally fed very low birth weight infants. In B. Koletzko, B. Poindexter, & R. Uauy (Eds.), *Nutritional care of preterm infants: Scientific basis and practical guidelines* (pp. 297–299). Basel, Switzerland: Karger.

Koo, W. W. K., & Hockman, E. M. (2006). Posthospital discharge feeding for preterm infants: Effects of standard compared with enriched milk formula on growth, bone mass, and body composition. *American Journal of Clinical Nutrition, 84*(6), 1357–1364. doi:10.1093/ajcn/84.6.1357

Lapillonne, A. (2014). Enteral and parenteral lipid requirements of preterm infants. In B. Koletzko, B. Poindexter, & R. Uauy (Eds.), *Nutritional care of preterm infants: Scientific basis and practical guidelines* (pp. 82–98). Basel, Switzerland: Karger.

Leaf, A., & Lansdowne, Z. (2014). Vitamins-Conventional uses and new insights. In B. Koletzko, B. Poindexter, & R. Uauy (Eds.), *Nutritional care of preterm infants: Scientific basis and practical guidelines* (pp. 152–166). Basel, Switzerland: Karger.

Litman, R. S., Smith, V. I., & Mainland, P. (2018). New solutions to reduce wrong route medication errors. *Pediatric Anesthesia, 28*(1), 8–12. doi:10.1111/pan.13279

Lucas, A., Fewtrell, M. S., Morley, R., Singhal, A., Abbott, R. A., Isaacs, E., . . . Clements, H. (2001). Randomized trial of nutrient-enriched formula versus standard formula for postdischarge preterm infants. *Pediatrics, 108*(3), 703–711. doi:10.1542/peds.108.3.703

Mahe, M. M., Helmrath, M. A., & Shroyer, N. F. (2017). Organogenesis of the gastrointestinal tract. In R. A. Polin, S. H. Abman, D. H. Rowitch, W. E. Benitz, & W. W. Fox (Eds.), *Fetal and neonatal physiology* (5th ed., pp. 861–870). Philadelphia, PA: Elsevier.

Margolis, K. G., & Picoraro, J. A. (2017). Development of gastrointestinal motility. In R. A. Polin, S. H. Abman, D. H. Rowitch, W. E. Benitz, & W. W. Fox (Eds.), *Fetal and neonatal physiology* (5th ed., pp. 881–888). Philadelphia, PA: Elsevier.

Marquardt, M. L., Done, S. L., Sandrock, M., Berdon, W. E., & Feldman, K. W. (2012). Copper deficiency presenting as metabolic bone disease in extremely low birth weight, short-gut infants. *Pediatrics, 130*, e695–e698. doi:10.1542/peds.2011-1295

Martin, R. J. (2017). Pathophysiology of apnea of prematurity. In R. A. Polin, S. H. Abman, D. H. Rowitch, W. E. Benitz, & W. W. Fox (Eds.), *Fetal and neonatal physiology* (5th ed., pp. 1595–1604). Philadelphia, PA: Elsevier.

Mead Johnson Nutrition. (2019, June 17). Professional center, product information. Retrieved from https://www.meadjohnson.com/brands/products-by-need#nutritionforpretermandlowbirthweightbabies

Meetze, W. H., Valentine, C., McGuigan, J. E., Conlon, M., Sacks, N., & Neu, J. (1992). Gastrointestinal priming prior to full enteral nutrition in very low birth weight infants. *Journal of Pediatric Gastroenterology and Nutrition, 15*(2), 163–170. doi:10.1097/00005176-199208000-00011

Meinzen-Derr, J., Poindexter, B., Wrage, L., Morrow, A., Stoll, B., & Donovan, E. F. (2009). Role of human milk in extremely low birth weight infants' risk of necrotizing enterocolitis or death. *Journal of Perinatology, 29*, 57–62. doi:10.1038/jp.2008.117

Mitchell, S. M., Rogers, S. P., Hicks, P. D., Hawthorne, K. M., Parker, B. R., & Abrams, S. A. (2009). High frequencies of elevated alkaline phosphatase activity and rickets exist in extremely low birth weight infants despite current nutritional support. *BMC Pediatrics, 9*, 47. doi:10.1186/1471-2431-9-47

Morgan, J., Bombell, S., & McGuire, W. (2013). Early trophic feeding versus enteral fasting for very preterm or very low birth weight infants. *Cochrane Database of Systematic Reviews*, (3), CD000504. doi:10.1002/14651858.CD000504.pub.4

Moya, F., Sisk, P. M., Walsh, K. R., & Berseth, C. L. (2012). A new liquid human milk fortifier and linear growth in preterm infants. *Pediatrics, 130*(4), e928–e935. doi:10.1542/peds.2011-3120

Namgung, R., & Tsang, R. C. (2017). Neonatal calcium, phosphorus, and magnesium homeostasis. In R. A. Polin, S. H. Abman, D. H. Rowitch, W. E. Benitz, & W. W. Fox (Eds.), *Fetal and neonatal physiology* (5th ed., pp. 881–888). Philadelphia, PA: Elsevier.

Nathan, A. T., Ward, L., Schibler, K., Moyer, L., South, A., & Kaplan, H. C. (2018). A quality improvement initiative to reduce necrotizing enterocolitis across hospital systems. *Journal of Perinatology, 38*, 742–750. doi:10.1038/s41372-018-0104-0

Neu, J. (2009). Is it time to stop starving premature infants? *Journal of Perinatology, 29*, 399–400. doi:10.1038/jp.2009.46

Neu, J. (2017). Digestive-absorption functions in fetuses. Infants, and children. In R. A. Polin, S. H. Abman, D. H. Rowitch, W. E. Benitz, & W. W. Fox (Eds.), *Fetal and neonatal physiology* (5th ed., pp. 897–905). Philadelphia, PA: Elsevier.

O'Connor, D. L., Khan, S., Weishuhn, K., Vaughan, J., Jefferies, A., Campbell, D. M., . . . Whyte, H. (2008). Growth and nutrient intakes of human milk-fed preterm infants provided with extra energy and nutrients after hospital discharge. *Pediatrics, 121*(4), 766–776. doi:10.1542/peds.2007-0054

Oddie, S. J., Young, L., & McGuire, W. (2017). Slow advancement of enteral feed volumes to prevent necrotizing enterocolitis in very low

birth weight infants. *Cochrane Database of Systematic Reviews*, (B), CD001241. doi:10.1002/14651858.CD001241.pub7

Olsen, I. E., Groveman, S. A., Lawson, L., Clark, R. H., & Zemel, B. S. (2010). New intrauterine growth curves based on United States data. *Pediatrics, 125*(2), e214–e224. doi:10.1542/peds.2009-0913

Parry, R. L. (2017). Development of the neonatal gastrointestinal tract. In R. A. Polin, S. H. Abman, D. H. Rowitch, W. E. Benitz, & W. W. Fox (Eds.), *Fetal and neonatal physiology* (5th ed., pp. 1364–1370). Philadelphia, PA: Elsevier.

Patole, S. K., & de Klerk, N. (2005). Impact of standardised feeding regimens on incidence of neonatal necrotising enterocolitis: A systematic review and meta-analysis of observational studies. *Archives of Disease in Childhood. Fetal and Neonatal Edition, 90*(2), F147–F151. doi:10.1136/adc.2004.059741

Poindexter, B. B., & Ehrenkranz, R. A. (2015). Nutrition requirements and provision of nutritional support in the premature neonate. In R. J. Martin, A. A. Fanaroff, & M. C. Walsh (Eds.), *Fanaroff and Martin's neonatal-perinatal medicine: Diseases of the fetus and infant* (10th ed., pp. 592–612). Philadelphia, PA: Elsevier.

Poindexter, B. B., Langer, J. C., Dusick, A. M., & Ehrenkranz, R. A. (2006). Early provision of parenteral amino acids in extremely low birth weight infants: Relation to growth and neurodevelopmental outcome. *Journal of Pediatrics, 148*(3), 300–305. doi:10.1016/j.jpeds.2005.10.038

Premji, S. S., & Chessell, L. (2011). Continuous nasogastric milk feeding versus intermittent bolus milk feeding for premature infants less than 1500 grams. *Cochrane Database of Systematic Reviews*, (11), CD001819. doi:10.1002/14651858.CD001819.pub2

Premkumar, M. H., & Calkins, K. L. (2018). A neonatologist's perspective: Is the quest for an "Ideal" lipid emulsion over? *Journal of Parenteral and Enteral Nutrition, 42*(1), 12–13. doi:10.1002/jpen.1027

Premkumar, M. H., Carter, B. A., Hawthorne, K. M., King, K., & Abrams, S. A. (2014). Fish oil-based lipid emulsions in the treatment of parenteral nutrition-associated liver disease: An ongoing positive experience. *Advances in Nutrition, 5*(1), 65–70. doi:10.3945/an.113.004671

Prolacta Bioscience. (2018). Products. Prolact+H2MF® nutrition information. Retrieved from https://www.prolacta.com

Radmacher, P. G., Lewis, S. L., & Adamkin, D. H. (2009). Early amino acids and the metabolic response of ELBW infants (≤1000 g) in three time periods. *Journal of Perinatology, 29*, 433–437. doi:10.1038/jp.2009.36

Ridout, E., Melara, D., Rottinghaus, S., & Thureen, P. J. (2005). Blood urea nitrogen concentration as a marker of amino-acid intolerance in neonates with birth weight less than 1250 g. *Journal of Perinatology, 25*, 130–133. doi:10.1038/sj.jp.72111215

Riskin, A., Cohen, K., Kugelman, A., Toropine, A., Waseem, S., & Bader, D. (2017). The impact of routine evaluation of gastric residual volumes on the time to achieve full enteral feeding in preterm infants. *Journal of Pediatrics, 189*, 128–134. doi:10.1016/j.jpeds.2017.05.054

Rogers, S. P., Hicks, P. D., Hamzo, M., Veit, L. E., & Abrams, S. A. (2010). Continuous feedings of fortified human milk lead to nutrient losses of fat, calcium and phosphorous. *Nutrients, 2*(3), 230–240. doi:10.3390/nu2030240

Sapsford, A., & Smith, C. (2016). Enteral nutrition. In Pediatric Nutrition Dietetic Practice Group, S. Groh-Wargo, M. Thompson, & J. H. Cox (Eds.), *Academy of Nutrition and Dietetics pocket guide to neonatal nutrition* (2nd ed., pp. 76–124). Chicago, IL: Academy of Nutrition and Dietetics.

Schanler, R. J., & Anderson, D. M. (2008). Nutrition support of the low birth weight infant. In C. Duggan, J. B. Watkins, & W. A. Walker (Eds.), *Nutrition in pediatrics* (4th ed., pp. 377–394). Hamilton, ON: BC Decker.

Schanler, R. J., Shulman, R. J., & Lau, C. (1999). Feeding strategies for premature infants: Beneficial outcomes of feeding fortified human milk versus preterm formula. *Pediatrics, 103*(6), 1150–1157. doi:10.1542/peds.103.6.1150

Senterre, T. (2014). Practice of enteral nutrition in very low birth weight and extremely low birth weight infants. In B. Koletzk, B. Poindexter, & R. Uauy (Eds.), *Nutritional care of preterm infants: Scientific basis and practical guidelines* (pp. 201–214). Basel, Switzerland: Karger.

Shulman, R. J. (1989). Zinc and copper balance studies in infants receiving total parenteral nutrition. *American Journal of Clinical Nutrition, 49*(5), 879–883. doi:10.1093/ajcn/49.5.879

Shulman, R. J., Ou, C. N., & Smith, E. O. (2011). Evaluation of potential factors predicting attainment of full gavage feedings in preterm infants. *Neonatology, 99*, 38–44. doi:10.1159/000302020

Shulman, R. J., & Phillips, S. (2003). Parenteral nutrition in infants and children. *Journal of Pediatric Gastroenterology and Nutrition, 36*, 587–607. doi:10.1097/00005176-200305000-00002

Shulman, R. J., Schanler, R. J., Lau, C., Heitkemper, M., Ou, C.-N., & Smith, E. O. (1998a). Early feeding, antenatal glucocorticoids, and human milk decrease intestinal permeability in preterm infants. *Pediatric Research, 44*, 519–523. doi:10.1203/00006450-199810000-00009

Shulman, R. J., Schanler, R. J., Lau, C., Heitkemper, M., Ou, C.-N., & Smith, E. O. (1998b). Early feeding, feeding tolerance, and lactase activity in preterm infants. *Journal of Pediatrics, 133*(5), 645–649. doi:10.1016/S0022-3476(98)70105-2

Sisk, P. M., Lovelady, C. A., Dillard, R. G., Gruber, K. J., & O'Shea, T. M. (2007). Early human milk feeding is associated with a lower risk of necrotizing enterocolitis in very low birth weight infant. *Journal of Perinatology, 27*, 428–433. doi:10.1038/sj.jp.7211758

Soghier, L. M., & Brion, L. P. (2010). Cysteine, cystine or N-acetylcysteine supplementation in parenterally fed neonates. *Cochrane Database of Systematic Reviews*, (4), CD004869. doi:10.1002/14651858.CD004869.pub2

Sohn, K., Kalanetra, K. M., Mills, D. A., & Underwood, M. A. (2016). Buccal administration of human colostrum: Impact on the oral microbiota of premature infants. *Journal of Perinatology, 36*, 106–111. doi:10.1038/jp.2015.157

Stephens, B. E., Walden, R. V., Gargus, R. A., Tucker, R., McKinley, L., Mance, M., . . . Vohr, B. R. (2009). First-week protein and energy intakes are associated with 18-month developmental outcomes in extremely low birth weight infants. *Pediatrics, 123*(5), 1337–1343. doi:10.1542/peds.2008-0211

Sullivan, S., Schanler, R. J., Kim, J. H., Patel, A. L., Trawoger, R., Kiechi-Kohlendorfer, U., . . . Lucas, A. (2010). An exclusively human milk-based diet is associated with a lower rate of necrotizing enterocolitis than a diet of human milk and bovine milk-based products. *Journal of Pediatrics, 156*(4), 562–567. doi:10.1016/j.jpeds.2009.10.040

Thureen, P. J., Melara, D., Fennessey, P. V., & Hay, W. W. (2003). Effect of low versus high intravenous amino acid intake on very low birth weight infants in the early neonatal period. *Pediatric Research, 53*, 24–32. doi:10.1203/01.PDR.0000042441.34920.77

U.S. Food & Drug Administration. (n.d.). Drugs@FDA: FDA approved drug products: Omegaven. Retrieved from https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=210589

Valentine, C. J., Fernandez, S., Rogers, L. K., Gulati, P., Hayes, J., Lore, P., . . . Welty, S. E. (2009). Early amino-acid administration improves preterm infant weight. *Journal of Perinatology, 29*, 428–432. doi:10.1038/jp.2009.51

Vanek, V. W. (2015). Review of trace mineral requirements for preterm infants: What are the current recommendations for clinical practice? *Nutrition in Clinical Practice, 30*(1), 720–721. doi:10.1177/0884533614563353

Vanek, V. W., Borum, P., Buchman, A., Fessler, T. A., Howard, L., Jeejeebhoy. K.,. . . American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Board of Directors. (2012). A.S.P. E.N. position

paper: Recommendations for changes in commercially available parenteral multivitamin and multi-trace element products. *Nutrition in Clinical Practice, 27*(4), 440–491. doi:10.1177/0884533612446706

van Goudoever, J. B., Vlaardingerbroek, H., van den Akker, C. H., de Groof, F., & van der Schoor, S. R. D. (2014). Amino acids and proteins. In B. Koletzko, B. Poindexter, & R. Uauy (Eds.), *Nutritional care of preterm infants: Scientific basis and practical guidelines* (pp. 49–63). Basel, Switzerland: Karger.

Verma, A., & Dhanireddy, R. (1993). Tine of first stool in extremely low birth weight (<1000 grams) infants. *Journal of Pediatrics, 122*(4), 626–629. doi:10.1016/S0022-3476(05)83550-4

Villar J., Giuliani, F., Bhutta, Z. A., Bertino, E., Ohuma, E. O., Ismail, L. C., . . . Kennedy, S. H. (2015). Postnatal growth standards for preterm infants: The preterm postnatal follow-up study of the INTERGROWTH-21st Project. *The Lancet: Global Health, 3*(11), e681–e691. doi:10.1016/S2214-109X(15)00163-1

Villar, J., Giuliani, F., Fenton, T. R., Ohuma, E. O., Ismail, I. C., & Kennedy, S., H. (2016). INTERGROWTH-21st very preterm size at birth reference charts. *The Lancet, 387*(10021), 844–845. doi:10.1016/S0140-6736(16)00384-6

Vlaardingerbroek, H., Vermeulen, M. J., Rook, D., van den Akker, C. H. P., Dorst, K., Wattimena, A. V., . . . van Goudoever, J. B. (2013). Safety and efficacy of early parenteral lipid and high-dose amino acid administration to very low birth weight infants. *Journal of Pediatrics, 163*(3), 638–644. doi:10.1016/j.jpeds.2013.03.059

Vohr, B. R., Poindexter, B. B., Dusick A. M., McKinley, L. T., Higgins, R. D., Langer, J. C., & Poole, W. K. (2007). Persistent beneficial effects of breast milk ingested in the neonatal intensive care unit on outcomes of extremely low birth weight infants at 30 months of age. *Pediatrics, 120*(4), e953–e959. doi:10.1542/peds.2006-3227

Watson, J., & McGuire, W. (2013). Transpyloric versus gastric tube feeding for preterm infants (Review). *Cochrane Database of Systematic Reviews*, (2), CD003487. doi:10.1002/14651858.CD003487.pub3

Wilson-Costello, D., Kliegman, R. M., & Fanaroff, A. A. (2013). Nutrition and selected disorders of the gastrointestinal tract, Part Three: Necrotizing enterocolitis. In A. A. Fanaroff & J. M. Fanaroff (Eds.), *Klaus & Fanaroff's care of the high-risk neonate* (pp. 193–200). Philadelphia, PA: Elsevier Saunders.

CHAPTER 21

Neonatal and Infant Pharmacology

Beth Shields

INTRODUCTION

Neonatal and infant pharmacology requires an understanding of the impact of immature organ systems on pharmacologic drug response. Research in pharmacology has lagged behind the enhanced survival rates for sick newborn infants of all birth weight subgroups. Optimal understanding of infant pharmacology is of vital importance, as the average number of drugs administered to premature infants weighing less than 1,000 g ranges from 15 to 20. Rapidly changing physiologic characteristics contribute to unpredictable dose response relationships. It is not always appropriate to determine neonatal dosing through extrapolation from childhood or adult studies. Few well-controlled trials or road maps outline the use of medications in this high-risk patient population (Ku & Smith, 2015). This chapter reviews the basic principles of neonatal and infant drug therapy. Discussion of the nursing implications is included.

DRUG THERAPY: EVIDENCE-BASED MEDICINE

The individualization of drug therapy in premature and term infants is essential because of rapid and variable maturation of all physiologic and pharmacologic processes. The phrase *therapeutic orphans*, coined many years ago, stresses the relative lack of drug safety and efficacy information in the pediatric population (Shirkey, 1968). Fifty years later, published literature on the use of medications in the neonatal population remains sparse. Conducting well-controlled trials is difficult, and therapeutic regimens are often supported by case reports, small studies, or past experiences of a particular clinician (Laforgia et al., 2014; Neville et al., 2014; O'Hara, Wright, & Schneider, 2015). Advances in clinical medicine, study design, and sampling and analytical techniques are assisting in moving the concept of therapeutic orphans to a more historical perspective (Ku & Smith, 2015; Reed, 2011).

PEDIATRIC LABELING

The Food and Drug Administration (FDA) approves the initial labeling of medication. Since the early 1970s, over 75% of medications approved have no pediatric indications. However, once a drug is FDA approved, it may be prescribed by a licensed provider for any indication deemed appropriate. Most infants in the neonatal intensive care unit (NICU) are prescribed at least one medication that is used off-label, that is, the use of a medication in any age group for a condition that is not included in the medical labeling (Krzyaniak, 2016; Laforgia et al., 2014; Rumore, 2016). Over the past 10 years, increased federal legislation has been passed to encourage the collection of safety, pharmacogenomic, pharmacokinetic, and pharmacodynamic data to aid in pediatric-specific labeling for medications. The Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) are important pieces of legislation with an emphasis on therapeutic areas and specific pediatric subpopulations. The passage of BPCA and PREA has resulted in more than 500 pediatric labeling changes. BPCA provides financial incentive to drug companies that test medications with a remaining patent in pediatric patients. PREA requires pediatric testing for new drug applications (Neville et al., 2014; Wharton, 2014). A list of drugs with a current exclusivity provision is outlined in the Pediatric Exclusivity Provision Best Pharmaceuticals for Children Act List of Pediatric Therapeutic Needs, June 2017, www.bpca.nichd.nih.gov.

PEDIATRIC DOSING METHODS

Infants are not small adults, and, as such, cannot simply be given a portion of an adult dose. Drug dosages must be prescribed for each infant on an individual basis. Their unique pharmacotherapeutic requirements predispose this population to errors in individual dosage calculations. Guidelines have been developed in an attempt to prevent dosing errors in this diverse patient population (Riley & Meyers, 2016; The Joint Commission, 2008). Several dosing methods have been used to calculate the optimal drug dose for both preterm and full-term infants. Pediatric dosage handbooks employ dosing methods based on age, body weight, and body surface area (BSA) as well as pharmacokinetic dosing (Reed, 2011; Taketomo, 2017; www.neofax.micromedexsolutions.com). Each method provides only an estimate, and dosages must constantly be reevaluated and adjusted according to clinical efficacy and toxicity. To calculate a drug dosage based on age or body weight, it is important to understand the meaning of terms commonly used in the pediatric population (Table 21.1). Because of the ease of calculation, dosing based on weight (mg/kg/dose or mg/kg/d) is the most common method. Weight-based dosing is expressed as a dosage range versus an absolute dose. In recent years, there has been an increased emphasis on the use of metric units only for weight-based dosing

TABLE 21.1

PEDIATRIC DRUG DOSING: AGE/WEIGHT TERMINOLOGY

Term	Definition
Gestational Age	By dates: number of weeks from the onset of mother's last menstrual period until birth
	By examination: assessment of gestation (time from conception until birth) by a physical and neuromuscular examination
Low birth weight	Birth weight of <2,500 g
Very low birth weight	Birth weight of <1,500 g
Small for gestational age	Birth weight <10th percentile for GA
Appropriate for gestational age	Birth weight between 10th and 90th percentile for GA
Large for gestational age	Birth weight >90th percentile for GA
PNA	Chronologic age (in days) after birth
Postconceptional age	GA at birth plus PNA
Preterm infant	<37 completed weeks' GA at birth
Full-term infant	38–42 weeks' GA at birth
Neonate	0–28 days PNA
Infant	1 month to 1 year of age
Child	1–12 years of age

GA, gestational age; PNA, postnatal age.

Source: Adapted from Engle, W. A., Blackmon, L. R., Batton, D. G., Bell, E. F., Denson, S. E., Kanto, W. P., Jr., . . . Stark, A. (2004). Age terminology during the perinatal period. *Pediatrics, 114*(5), 1326–1364 (reaffirmed July 2014). doi:10.1542/peds.2004-1915.

(American Academy of Pediatrics [APA], 2017, Institute for Safe Medication Practices [ISMP], 2017). Dosing based on BSA (mg/m^2/dose) requires both a weight and height to accurately assess an infant's BSA. Lack of appropriate pediatric dosing information makes this method impractical, and it has not been shown to increase accuracy or safety (O'Hara et al., 2015).

ADVERSE DRUG EFFECTS

Like the elderly, infants are prone to adverse drug effects (ADEs). An ADE is an injury (both preventable and not preventable) that results from the use of a drug (Allegaert & van den Anker, 2014). Unique drug delivery factors, including individual dosage calculations, preparation of small doses from concentrated commercial solutions, multiple commercial concentrations, and slow intravenous (IV) rates, make neonates more prone to ADEs. Neonates are particularly predisposed to ADEs because of immature metabolic and excretion pathways as well as potential drug exposures during pregnancy, delivery, and lactation. In some instances, medications used for years have come into question. For example, acetaminophen with codeine products, commonly prescribed for pain in the postpartum period, have recently been shown to have the potential for central nervous system (CNS) depression and apnea in a cohort of breastfed infants. In addition, a strengthened warning against the use of tramadol in breastfed women had been added by the FDA. Such adverse effects may be related to unique metabolic pathways in some mothers (FDA, 2017).

Several classic neonatal ADEs have occurred because of lack of knowledge or forethought regarding developmental differences between neonates and older infants and children. Examples of such ADEs include chloramphenicol-associated gray baby syndrome, neonatal gasping syndrome, and numerous case reports of ADEs caused by absorption of drugs through the skin of newborn infants (Robertson, 2003a, 2003b). The enhanced survival of extremely premature infants must raise awareness concerning the increased risk of serious short- and long-term adverse effects of neonatal drug therapy. Data support an increased incidence of neurodevelopmental delay and cerebral palsy in infants treated with high-dose systemic dexamethasone in an attempt to decrease the incidence of bronchopulmonary dysplasia (Watterberg et al., 2010).

MEDICATION ERRORS

Medication errors in the neonatal population are an iatrogenic cause of ADEs. Such errors have been noted at a rate three to eight times that published in the adult patient population. It is estimated that one fifth to one half of all medication errors in a pediatric hospital occur in the NICU (Poole & Carleton, 2008). Medication errors can occur at any stage of the medication use process. Errors are particularly high risk in the neonatal population due to the need for multiple dosing calculations; wide weight ranges; immature renal, hepatic, and immune pathways; and extended lengths of stay. Prevention strategies include collaborative efforts of a multidisciplinary healthcare team, use of computerized physician order entry systems, barcode medication administration, standardization of doses and medication concentrations, and provision of measuring tools that more closely match prescribed volumes for oral medications (APA, 2017; The Joint Commission, 2008; Krzyaniak, 2016, Krzyaniak & Bajorek, 2016; Paul et al., 2015; Rinke et al., 2014; Rostas, 2017; Sauberan, Dean, Fiedelak, & Abraham, 2010; Yin et al., 2017). Each year, the ISMP lists best practices, many of which are pertinent to the NICU (Box 21.1).

The use of standard IV and oral compound concentrations is suggested by both ISMP and The Vermont Oxford Network (VON) for the neonatal patient population (Phillips, 2011). In addition, Standardize for Safety is an initiative to reduce IV and oral liquid medication errors and to standardize concentrations through transitions of care (American Society of Health System Pharmacists, 2016).

Inadvertent overdoses of heparin gained a great deal of press in neonatal literature. Heparin is on the ISMP high-alert list and can cause considerable patient harm. In addition to the issues outlined earlier, stocking of look-alike products with 100- or 1,000-fold strength differences has contributed to these errors (Monagle, Studdert, & Newall, 2011; Riley & Meyers, 2016). Changes in packaging have resulted from the medication errors with heparin.

Box 21.1

2018–2019 TARGETED MEDICATION SAFETY BEST PRACTICES FOR HOSPITALS

Measure and document patient weights in metric units, kilograms, only.

- Modify scales to lock out the ability to weigh in pounds (lb)
- Have conversion charts that convert from kilograms (or grams for pediatrics) to lb near all scales so parents can be told the weight in lb
- Ensure computer information system screens (i.e., infusion pumps) prompt for weights in metric units only

Purchase oral liquid devices (oral syringes) that display only the metric scale (mL).

- For discharge, provide parents with oral syringes that measure liquid volumes in mL
- Ensure that oral liquid medications not commercially available in unit dose packaging are dispensed by the pharmacy in an oral or ENFit syringe

Segregate and differentiate neuromuscular blocking agents from other medications.

- Standardize storage and clearly label with auxiliary stickers

Administer high-alert intravenous (IV) medication infusions via a programmable infusion pump utilizing dose error-reduction software.

- Smart pumps with drug libraries

When compounding sterile preparations, perform independent verifications to ensure appropriate volumes of medications and diluents (volume) prior to addition to the final container.

- At a minimum, perform this verification for all high-alert medications, as well as pediatric and neonatal preparations

Note: Focus on those recommendations pertinent to the neonatal patient population.

Source: Institute for Safe Medication Practices. (2017). Targeted medication safety best practices for hospitals. Retrieved from https://www.ismp.org/guidelines/best-practices-hospitals

Many institutions now use checklists for medications, requiring two people to review the orders and what is to be administered before the medication is actually given. Medication Administration Records and physician order entry systems now have built-in checks and balances for drug incompatibilities and wrong dosages. A required system override is necessary in order to dispense a drug that is not considered within a safe range. That being said, many institutions have not used these electronic systems, and systems are only as good as the information that is included in the database.

DEVELOPMENTAL PHARMACOKINETICS

Pharmacokinetics is the study of a drug concentration versus time, and encompasses the four major processes of absorption, distribution, metabolism, and elimination (ADME) of a drug and its metabolites in the body. Developmental pharmacokinetics—or the change in the ADME of drugs with organ maturation—is a well-known phenomenon (Figure 21.1). To fully comprehend the ADME of drugs, pharmacokinetic terminology must be applied. Standard pharmacokinetic terminology is used when describing the ADME of medications (Table 21.2). In addition to the pharmacokinetics of a drug, the pharmacodynamics of a particular medication is also important. Pharmacodynamics is the relationship between the pharmacokinetics of a drug and its therapeutic or toxic effects in a specific patient. Pediatric drug-dosing regimens are influenced by both the effect of the body on a drug (pharmacokinetics) and the effect of a drug on the body (pharmacodynamics). Data support age-dependent differences in the interaction of a drug and its receptors, ultimately resulting in an altered pharmacodynamic response (Kearns et al., 2003).

Absorption

Absorption refers to the translocation of a drug from the site of administration into the systemic circulation. With the exception of the IV route, all other routes of administration require a drug to cross membranes in order to reach the systemic circulation and exert its pharmacologic effects. Bioavailability is the pharmacokinetic term that has been used to describe the extent to which a drug enters the systemic circulation (Soldin & Soldin, 2002). Drugs administered via the IV route are 100% bioavailable and delivered directly to the bloodstream. Drug absorption depends on the physiochemical properties of the drug—including molecular weight, degree of ionization, lipid solubility, and drug formulation characteristics. In addition, patient-dependent factors, many of which are age related, affect drug absorption (Johnson, 2011; Kearns et al., 2003).

Medications are administered to infants via many routes including oral (PO), IV, intramuscular (IM), intraosseous (IO), percutaneous, intranasal, rectal, intratracheal, and inhalation. There has been an increased use of intranasal administration in older infants for procedural sedation and refractory seizures, as well as cases where IV access is difficult. Parenteral administration (IV) of drugs is important when a rapid response is desired or clinical status precludes oral absorption. Muscle tone, muscle mass, and regional blood flow to the area influence absorption of medications from an IM injection. Neonates, particularly premature neonates, may have significantly decreased muscle mass, as muscle mass is directly proportional to an infant's gestational age (GA; Kearns et al., 2003). The IM injection of a medication may result in a delay in peak serum concentrations due to poor or erratic absorption. Medications commonly administered to neonates via the IM route include vitamin K, ampicillin, and gentamicin.

Absorption from the gastrointestinal tract depends on factors including gastric acidity, gastric emptying time, bacterial colonization of the gastrointestinal tract, intestinal transit time, biliary and pancreatic function, and the type of infant milk diet (Johnson, 2011; Kearns et al., 2003; O'Hara et al., 2015). The maturation of gastric pH differs in preterm versus term infants and seems to correlate with postnatal age rather than postconceptional age. The gastric pH at birth approaches 6 to 8 because of the presence of residual amniotic fluid, falls to approximately 1.5 to 3 several hours after birth, and then slowly increases over the next 10 days in term infants. The lack of gastric acid output early in postnatal life is called relative achlorhydria. Gastric pH will reach adult values by 2 years of age (Woo, 2004). Gastric pH affects drug ionization and drug absorption. A more basic environment (higher gastric pH) will decrease the absorption of acidic drugs (i.e., phenytoin, phenobarbital) and favor the oral absorption of more basic or acid-labile drugs (i.e., ampicillin, penicillin, and erythromycin).

Most drugs are absorbed in the small intestine. Therefore, gastric emptying time will play an important role in both the rate and

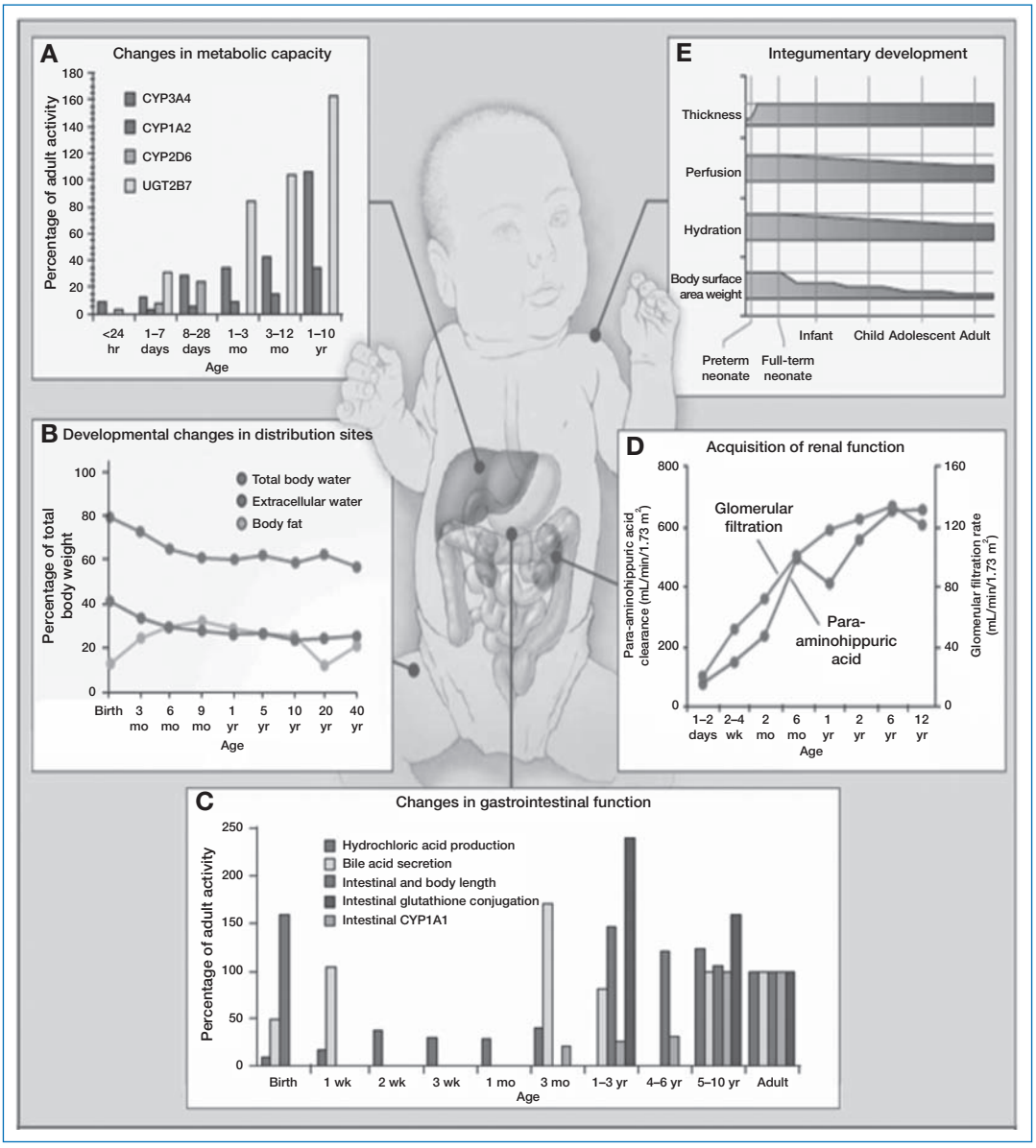


FIGURE 21.1 Age-dependent changes in both the structure and function of the gastrointestinal tract.

Source: Adapted from Kearns, G. L., Abdel-Rahman, S. M., Alander, S. W., Blowey, D. L., Leeder, J. S., & Kauffman, R. E. (2003). Developmental pharmacology—Drug disposition, action, and therapy in infants and children. *New England Journal of Medicine, 349*(12), 1157–1167. doi:10.1056/NEJMra035092.

extent of oral drug absorption. Gastric emptying time is delayed in the neonatal patient, especially in the premature infant. Gastric emptying may be prolonged up to 6 to 8 hours and may not attain adult values until 6 to 8 months of age. Oral absorption may also be delayed in the neonate because of decreased intestinal transit time and activity of pancreatic enzymes as well as low concentrations of intraluminal bile acids (Kearns et al., 2003; Woo, 2004).

Percutaneous absorption or absorption through the skin depends on skin integrity, blood flow to the skin, thickness of the epidermal layer (i.e., stratum corneum), skin hydration, and the ratio of surface area per kilogram of body weight (BSA-to-weight ratio). Percutaneous absorption may be increased substantially in newborn infants because of an underdeveloped stratum corneum, smaller amounts of subcutaneous fat, and increased skin hydration. Maturation of premature skin is related to postnatal age, and the attainment of an epidermal layer similar to that of a full-term neonate occurs within 3 weeks of postnatal life.

The greater the BSA to weight ratio, the greater the absorption of a drug is on a per-kilogram basis with topical medications. The ratio of a newborn's skin to BSA is approximately three times that of an adult. Systemic toxicity has been described in neonates after the administration of topical iodine, hexachlorophene, salicylic acid, epinephrine, and corticosteroids (O'Hara et al., 2015; Woo, 2004). The rectal mucosa may serve as a site of drug absorption in neonates who are unable to take medications by mouth, and in whom rapid IV access cannot be achieved. Rectal absorption depends on regional blood flow, retention of the drug in the rectum, and chemical properties of the drug. The rectal route of administration results in less efficient absorption when compared to the oral route, and in many instances higher mg/kg doses may be required. Medications commonly administered via the rectal route in infants include acetaminophen, diazepam, and sodium polystyrene sulfonate.

Distribution

Once a medication has reached the bloodstream, it will distribute among various organs, fluids, and tissues. The distribution of drugs within the body is influenced by many factors, including

TABLE 21.2

PHARMACOKINETIC TERMINOLOGY

Pharmacokinetic Term	Abbreviation	Definition
Bioavailability	F	The extent to which a drug enters the systemic circulation
Volume of distribution	Vd	The relation between the distribution amount of drug in the body and the measured plasma concentration
Clearance	Cl	The ability of eliminating organs to remove a drug from the blood or plasma
Elimination half-life	$t_{1/2s}$	The time required for half the amount of drug present in the blood to disappear
Steady-state concentration	Cpss	A concentration at which the rate of drug administration is equal to the rate of drug elimination

Source: Adapted from Soldin, O. P., & Soldin, S. J. (2002). Review: Therapeutic drug monitoring in pediatrics. *Therapeutic Drug Monitoring, 24*(1), 1–8. doi:10.1097/00007691-200202000-00001

total body water, total body fat, plasma and tissue binding, membrane permeability, and the infant's hemodynamic status. Drugs that are hydrophilic mainly distribute into body water, while lipophilic drugs preferentially distribute into fat. The pharmacokinetic term used to describe the relation between the amount of drug in the body and the measured plasma concentration is the apparent volume of distribution (Vd) (Johnson, 2011).

Total body water can be divided into intracellular and extracellular spaces. At birth, a full-term neonate is approximately 80% water, with 45% as extracellular and 35% as intracellular fluid. By 1 year of age, a child is approximately 60% water, with 20% extracellular and 40% intracellular fluid (Kearns et al., 2003) (Figure 21.1). Body fat is approximately 1% of the total body composition of a premature infant at 29 weeks' GA, increases to approximately 15% at term, and is 25% of total body composition between 1 and 2 years of age. Water-soluble medications have a much higher volume of distribution in neonates than in adults; therefore, neonatal dosing is higher on a per-kilogram basis (i.e., gentamicin, vancomycin). Fat-soluble medications have a much smaller distribution volume in a neonate than in an adult. Neonatal dosing of medications that are fat soluble is lower on a per-kilogram basis (Kearns et al., 2003; Woo, 2004).

Several physiologic variables can produce both quantitative and qualitative differences in plasma and tissue binding of drugs. In general, neonatal plasma protein binding of drugs is decreased in comparison to adults. The decrease in plasma protein binding in neonates is a result of several factors, including the decreased formation of plasma proteins by the immature neonatal liver. Albumin is the major drug-binding protein in plasma and binds primarily to acidic drugs (i.e., phenobarbital, phenytoin). A lower plasma pH may decrease protein binding of acidic drugs, and the presence of endogenous substances may compete for protein-binding sites. Endogenous substances in the neonate include free fatty acids and bilirubin, as well as transplacentally acquired interfering substances such as hormones and pharmacologic agents. Reduction in protein binding of drugs leads to an increase in the unbound or active component of the drug (Kearns et al., 2003; O'Hara et al., 2015).

Metabolism

Metabolism of drugs is necessary for both drug activity and clearance. Drug metabolism is influenced by genetic factors (pharmacogenomics), age, and the activity of drug-metabolizing enzymes. Most drugs are fat soluble and require biotransformation into more water-soluble substances before elimination from the body. This process of biotransformation occurs mainly in the liver, and produces active as well as inactive metabolites.

The two main types of drug metabolism are phase I (nonsynthetic) and phase II (synthetic) reactions. Phase I reactions include oxidation, reduction, methylation, hydrolysis, and hydroxylation. The cytochrome P450 mixed-function oxidase system is responsible for most phase I reactions. Phase II reactions include conjugation with glycine, glucuronic acid, and sulfate. Phase I reactions appear to mature more rapidly, meeting or exceeding adult capacity by 6 months of age.

Phase II reactions reach adult levels in children by 3 to 4 years of age. Maturation of these enzymatic pathways will affect neonatal metabolism of medications and thereby affect the clinical response to medications (Figure 21.1). **Emergency Alert: Examples of drug toxicity in neonates with immature metabolic pathways include the gray baby syndrome, caused by decreased capacity to glucuronidate chloramphenicol, as well as neonatal gasping syndrome, which results from the decreased capacity of infants to glycinate benzyl alcohol.** Benzyl alcohol is a preservative found in multidose medications and flush solutions (O'Hara et al., 2015; Robertson, 2003a).

Neonates may use different pathways to metabolize drugs than older infants and children use. These pathways may result in a modified pharmacologic response to medications. For example, neonates are not able to metabolize morphine adequately to its 6-glucuronide metabolite, a metabolite that is 20 times more active than morphine as an analgesic. Theophylline, a drug used for the treatment of apnea of prematurity, presents another example of altered metabolic pathways. Theophylline is oxidized to inactive components in adults but is *N*-methylated to caffeine, a pharmacologically active agent in the neonate.

Maturation of hepatic enzymes may also be influenced by prenatal or postnatal exposure to enzyme-inducing (i.e., phenobarbital, phenytoin, rifampin) or enzyme-inhibiting (i.e., erythromycin) agents. One drug may alter the metabolism of another medication, thereby increasing or decreasing effectiveness, creating toxicity, or producing subtherapeutic levels. Drug activity may also be interfered with by concurrent disease states. Interferences such as these are referred to as drug–disease state interactions (Kearns et al., 2003).

Elimination

Systemic clearance (Cl) is the ability of the eliminating organs (kidney, liver, lung, skin) to remove a drug from the blood or plasma. Drugs and their metabolites are primarily eliminated by the kidneys. The principal renal mechanisms responsible for drug excretion include glomerular filtration, tubular secretion, and

tubular reabsorption, all of which are immature at birth. Overall renal function increases with age, although as with hepatic metabolism, the maturation rate of individual physiologic functions varies (Figure 21.1). Glomerular filtration matures several months before tubular secretion; tubular reabsorption is the last to mature. The glomerular filtration is directly proportional to GA after 34 weeks' gestation. The increase in glomerular filtration after birth depends on postconceptional age and is influenced by increased cardiac output, decreased peripheral vascular resistance, increased mean arterial pressure, and increased surface area for filtration. The clinical importance of increases in glomerular filtration becomes apparent when one examines drugs excreted primarily by filtration such as gentamicin and vancomycin. Tubular reabsorption and secretion are also decreased in the neonate. Ampicillin, a drug commonly used in the neonatal population, undergoes tubular secretion (Woo, 2004).

The elimination half-life ($t_{1/2}$) of a drug refers to the time it takes for half the amount of drug in the blood to be eliminated. The volume of distribution and clearance of a medication are determinants of a drug's half-life. Half-life is an important factor in determining the appropriate interval between drug doses. Drugs with a long half-life are given at less frequent dosing intervals, whereas those with shorter half-lives may need to be given via a continuous infusion (Johnson, 2011).

With constant drug dosing, the elimination half-life will determine the time to reach the so-called steady-state serum concentration. Steady state refers to the time at which the rate of drug administration equals the rate of drug elimination. When drug concentrations are monitored in clinical practice, steady-state concentrations should be obtained. Steady-state concentrations are reached in approximately five half-lives. This factor explains the rationale for administering a loading dose for medications with long half-lives. A loading dose is a single dose of a medication that is used to rapidly attain a serum concentration and therefore the desired clinical effect. A loading dose produces a higher circulating concentration earlier in the therapeutic course as opposed to waiting five half-lives. In neonates, loading doses are commonly administered for caffeine, phenobarbital, phenytoin, digoxin, and levetiracetam (Johnson, 2011).

THERAPEUTIC DRUG MONITORING

Therapeutic drug monitoring (TDM) is the use of serum drug concentrations and pharmacokinetic and pharmacodynamic principles to regulate drug dosages. TDM is of particular importance in the neonatal population, which may under- or overrespond to the usual dosing regimens. Additional unique considerations in the neonate include the precise delivery of very small doses and volumes of medications, the availability of blood for measurement of drug concentrations, interference of endogenous substances with drug assays, frequent changes in neonatal pharmacokinetic parameters, and the extrapolation of therapeutic serum concentrations from adult data to the neonatal population (Fullas, Padomek, Thieman, & Van Gorp, 2011; Johnson, 2011; Touw, Westerman, & Sprij, 2009).

TDM is used for drugs in which a correlation between the measured plasma concentration and drug efficacy or toxicity exists. Drugs with narrow therapeutic indexes are ideal candidates for TDM. A drug exhibits a narrow therapeutic index if the plasma concentration required for therapeutic effects is relatively close to the concentration known to produce toxicity. Drugs for which TDM is used in the neonatal population include caffeine, phenobarbital, phenytoin, levetiracetam, gentamicin, tobramycin, amikacin, vancomycin, and digoxin. TDM allows the clinician to aim for a therapeutic range, which is usually safe and effective, with minimal drug toxicity.

With the exception of drugs administered via a continuous infusion, drug concentrations in the plasma are not static. The time of blood sampling relative to the time of drug administration is of utmost importance. For some medications, both trough and peak concentrations are monitored, whereas with other medications it is routine to monitor trough concentrations. Obtaining levels once a patient achieves steady-state concentrations provides the most accurate information with regard to drug efficacy or toxicity. Patients with altered organ function or rapidly changing clinical status may require closer monitoring of serum concentrations than do other patients.

Certain medications such as phenytoin are highly plasma protein–bound. For these medications, two types of assays are available: total and free serum concentrations. Free levels indicate the amount of free, unbound drug that is available to exert its effects on target tissues. When free phenytoin serum assays are not available, caution must be used in the interpretation of total serum concentrations. Levels may be falsely interpreted as low when the actual amount of active drug is adequate or toxic (Soldin & Soldin, 2002).

FETAL AND INFANT EXPOSURE TO MATERNAL MEDICATIONS

Fetal Exposure

Approximately 90% of women take one medication during pregnancy, with 70% taking at least one prescription medication. Over the last 30 years, the use of prescription medications during the first trimester has increased over 60%. Virtually any medication or substance given to the mother, either intentionally or inadvertently, can cross the placental membrane (Pernia & DeMaagd, 2016).

The amount of drug that passes into the fetal circulation depends on several factors, including the molecular weight, protein binding, lipid solubility, ionization of the drug, maternal drug serum concentrations, and integrity of the placental barrier. Physiologic changes during pregnancy can affect absorption, distribution, metabolism, and excretion of medications in the mother. Pregnancy results in many pharmacokinetic changes in the mother, including a greater volume of distribution, additional fat stores, and lower protein binding. Fetal exposure to a medication may lead to deleterious effects on the exposed fetus or may result in minimal or no adverse outcomes.

In recent years, the FDA has worked to collect and include more comprehensive information on drug labels regarding the drug's effects during pregnancy, including revisions to the product labeling (Food and Drug Administration, 2014). The Pregnancy and Lactation Labeling Rule (PLLR) or Final Rule, introduced by the FDA in 2014, addresses shortcomings in the current pregnancy category labeling, and strives to better convey the risks versus benefits during pregnancy and lactation. Over-the-counter (OTC) medications are not affected by the PLLR. The Females and Males of Reproductive Potential, new to the labeling, includes information about the need for pregnancy testing, contraception, and information about infertility as it relates to the drug. This information can assist healthcare providers in counseling pregnant women and nursing mothers who need to take medications (Pernia & DeMaagd, 2016; Ramoz & Patel-Shori, 2014). The PLLR removes pregnancy letter categories—A, B, C, D, and X—and requires the label to be updated when information becomes outdated (Table 21.3).

PLLR labeling changes came into effect on June 30, 2015. Prescription drugs and biologic products submitted after June 30,

TABLE 21.3

COMPARISON OF PREGNANCY AND LACTATION RULES 1979 VERSUS 2015

Rule in Phase Out	New Pregnancy and Lactation Label Ruling
Pregnancy risk categories (A, B, D, X) assigned	Pregnancy risk letter categories eliminated
Pregnancy Labor and delivery	Combined to form one section: Pregnancy • Pregnancy exposure registry • Risk summary • Clinical considerations and data
Nursing mothers	Lactation • Risk summary • Clinical considerations and data
	Females and males of reproductive potential • Pregnancy testing • Contraception and infertility

Source: Adapted from Pernia, S., & DeMaagd, G. (2016). The new pregnancy and lactation labeling rule. *Pharmacy and Therapeutics, 41*(11), 713–715. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5083079

2015, will use the new format immediately, while labeling for prescription drugs approved on or after June 30, 2001, will be phased in gradually (Table 21.4).

Lactation Exposure

An often-overlooked source of exposure to medications is transfer from the maternal circulation into breast milk. The lactation subsection provides information about using a drug while breastfeeding, such as the amount of drug in breast milk and potential effects on the breastfed infant. The safety and potential risks to the nursing infant must be considered during maternal drug use. Maternal drug use includes OTC drugs, prescription drugs, illicit drugs, and herbal products. The pH and size of a drug molecule, protein-binding properties, lipid and water solubility, and diffusion rate will all influence the quantity of drug that passes from maternal serum into breast milk. Additional considerations include the time the medication is taken in relation to the period of nursing, the dose and frequency of a medication, the pharmacokinetics of the drug, the length of nursing, and the amount of milk ingested. Published literature outlines guidelines regarding the transfer of drugs and chemicals into human milk. Only a small number of medications, including radiopharmaceuticals and chemotherapeutic medications, are considered contraindicated in the breastfeeding infant (Eidelman et al., 2012).

MEDICATION ADMINISTRATION

Once an appropriate drug dosage is established, the optimal route and method of drug administration are also of utmost importance. Many commercially available dosage forms are not suitable for use in the pediatric patient population. Developmental considerations with regard to medication administration must also be considered.

TABLE 21.4

IMPLEMENTATION SCHEDULE OF THE NEW PLLR

Applications for Drug or Biological Product	Compliance Requirements
Approved prior to June 30, 2001	Remove pregnancy category within 3 years of the effective date of PLLR. No other compliance requirements.
Approved June 30, 2001–June 29, 2002	3 years after the effective date of PLLR
Approved June 30, 2002–June 29, 2005	5 years after the effective date of PLLR
Approved June 30, 2005–June 29, 2007	3 years after the effective date of PLLR
Approved June 30, 2007–June 30, 2015	4 years after the effective date of PLLR
Pending approval on June 30, 2015	4 years after the effective date of PLLR or at time of approval, whichever is later
Submitted on or after June 30, 2015	Time of submission

PLLR, Pregnancy and Lactation Labeling Rule.

Source: From Pernia, S., & DeMaagd, G. (2016). The new pregnancy and lactation labeling rule. *Pharmacy and Therapeutics, 41*(11), 713–715. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5083079

Oral Administration

Many drugs prescribed for infants and children are not available in oral dosage forms that can be easily administered to small infants and children. Oral medications are administered to an infant via a nipple, dropper, syringe, or feeding tube. The preferred dosage form for infants is an alcohol-free, sugar-free, dye-free, and low-osmolality liquid preparation. However, orally administered medications may only be commercially available as tablets or capsules or as concentrated oral solutions or suspensions. **Quality and Safety: High-osmolality substances administered to the neonate have been associated with many adverse effects, including the development of necrotizing enterocolitis and decreased intestinal transit time.**

Preparation and delivery of small therapeutic doses from concentrated commercial oral solutions may be difficult. Alteration (dilution or compounding) of an adult dosage form raises issues regarding compatibility, stability, and the risk for medication errors. Commonly prescribed oral medications that are not commercially available in an appropriate liquid formulation include hydrocortisone, captopril, ursodiol, and spironolactone. Oral medications may also contain silent or inactive ingredients that supply the "delivery system" of the drug or serve to flavor, sweeten, and preserve the drug. Such inert ingredients may be harmless in adults but may, when administered frequently to neonates, result in toxicity (Mennella & Beauchamp, 2008; Robertson, 2003b). **Emergency Alert: An additional safety concern in the sick neonate is the inadvertent connection between an enteral feeding system and a nonenteral system such as an IV catheter (Box 21.2).**

Box 21.2

GLOBAL STANDARD (80369) TO REDUCE RISK OF TUBING MISCONNECTIONS: ENFIT

Approximately 10 years ago, an international group of manufacturers, clinicians, and regulators began collaborating with the International Organization of Standardization (ISO) and the Association for the Advancement of Medical Instrumentation (AAMI) to develop a new connector (ISO 80369 enteral and gastric design standards) to limit the ability to insert male connectors into female feeding ports; this initiative reverses the orientation of these oral connections.

The new standards will reduce the risk of connectors for two unrelated patient delivery systems being physically misconnected (Institute for Safe Medication Practices 2015; Skog, 2016). Enteral (feeding) Luer connections have been noted to have the highest rate of misconnections. California is the only state that required compliance by 2017, but other states are expected to follow behind. The Global Enteral Device Supplier Association (GEDSA) has launched a "Stay Connected" campaign to encourage participation in this medication safety initiative. Healthcare organizations must plan for a transition in the supply chain and train healthcare providers.

The federally registered trademark name for these new oral connections is ENFit. These new standards address dose accuracy with specific considerations for small doses in the neonatal population. Syringe sizes of 5 mL or less require ENFit Low Dose Tip Syringe design.

Source: Institute for Safe Medication Practices. (2015). *ENFit enteral devices are on their way...Important safety considerations for hospitals*. Retrieved from http://www.ismp.org/newsletters/acutecare/showarticle.aspx?id=105

Intravenous Administration

The most effective means of rapid drug delivery in a critically ill neonate is IV administration. As with oral medications, small doses and delivery volumes complicate the delivery of IV medications. Furthermore, IV medication delivery is often delayed, prolonged, or incomplete in the neonatal patient. A distal drug delivery site and slow infusion rates delay IV drug delivery. A major impact of delayed drug delivery is the potential for subtherapeutic plasma concentrations or even clinical failure with some medications. This is particularly important for medications that may require TDM. In addition, touch contamination, or the wrong delivery route or method, in the extremely vulnerable premature infants makes the use of closed IV systems of utmost importance. Central-line bundle initiatives have been instituted in many institutions in an effort to reduce central line–associated bloodstream infections (CLABSI; Taylor, McDonald, & Tan, 2015).

Several techniques are currently used to administer parenteral medications in the neonatal population and include IV push, IM, and use of smart infusion pumps. The infusion device, IV tubing, a container holding the medication (i.e., syringe, IV bag), dead space at injection ports, and IV in-line filters will affect drug delivery. Patient-specific factors such as body position and vascular occlusion may also affect IV drug delivery (Harding, 2011).

Administration of medications using the IV push method allows rapid drug delivery, but is not appropriate for many medications. Drug delivery with a smart IV infusion pump and microbore tubing is the preferred method of IV drug administration in the neonatal population. A syringe pump allows absolute control over the rate of drug delivery with minimal IV fluid volume, at a rate that is independent of the primary IV rate. Microbore tubing allows the use of minimal volumes of flush solution. In addition to intermittent medications, continuous infusion medications such as pressors and inotropes may be administered via a syringe pump. Smart pumps incorporate computer technology, allowing the use of drug libraries, standard drug concentrations, and sophisticated checks, including soft- and hard-dosing limits. A potential disadvantage of syringe pumps, in particular the smart pumps, is the capital expense required to purchase the pump (Harding, 2011).

Many of the problems that plague commercially available oral medications can also be found in commercial IV medications. IV medications may be available in concentrations that prohibit accurate measurement and administration of small neonatal doses. Use of standard parenteral concentrations in the neonatal population is highly recommended to decrease medication errors as well as continuity of medication therapy through transitions of care (http://ismp.org/newsletters/acutecare/showarticle.aspx?id=105). Continued work in standardizing concentration among all pediatric patients is ongoing, with final recommendations coming for all pediatric patients in the coming years. In selection of parenteral medications, not only drug concentration but also preservatives and other ingredients in the parenteral preparation are factors. Benzyl alcohol is a common preservative added to parenteral drug products. Severe toxicity has been reported in neonates after the use of flush solutions that contain benzyl alcohol. Whenever possible, preservative-free parenteral products should be used in the neonatal population for the first 2 months of life.

The osmolality of a drug solution is an important delivery factor. Tissue irritation or pain at the injection site can occur when a drug solution with an osmolality significantly different from that of the serum (275–295 mOsm/kg) is administered intravenously. As a point of reference, the osmolality of dextrose 10% in water, an IV solution used commonly in the newborn infant, is 505 mOsm/kg. Infiltration of a hypotonic or hypertonic solution can cause trauma and necrosis of the injection site (Beall, Mulholland, & Gephart, 2013; Murphy, Gilmour, & Coombs, 2017; Ramasethu, 2004).

Premature infants typically have fluid restrictions as well as limited IV access, and the question of IV drug compatibilities often comes into play. Drug compatibility involves the question of both physical (visual) and chemical (nonvisual) compatibilities. IV drug compatibility is not clear-cut. This is true because of the influence of alterations in drug concentration, order of drug infusion, pH, and temperature. For these reasons, reference books and articles may provide conflicting information with regard to drug compatibilities. Two drugs are physically incompatible when turbidity, cloudiness, or a precipitate is formed after two or more drugs are mixed together. A physical incompatibility results when calcium gluconate and sodium bicarbonate–containing or phosphorus-containing solutions are mixed in the same IV solution or IV tubing. Chemical incompatibility implies a loss of potency or formation of a toxic byproduct when two or more substances are mixed. Epinephrine and sodium bicarbonate are chemically incompatible when co-infused (Taketomo, 2017; Trissel, 2016).

Extravasation and infiltration are used interchangeably in the literature; both terms reflect a leakage of IV fluid or medication out of a vein and into surrounding tissues (Gil, Shah, Suarez, & Weiss, 2017; Ramasethu, 2004). Extravasation in neonates with circulatory compromise can lead to significant morbidity, functional impairment, or cosmetic defects. Many medications (i.e., potassium, calcium, parenteral nutrition, and dopamine) that are incorporated into the drug regimens of patients in the NICU are

capable of causing tissue damage if extravasation occurs. The use of small or superficial venous access sites in areas that are difficult to immobilize should be avoided for administration of these agents unless absolutely necessary. Particularly tenuous sites include areas surrounding tendons, nerves, or arteries or near the face and forehead. The degree of cellular injury is often directly related to the physiochemical characteristics of the infusant—including osmolarity, pH, molecular weight, volume and location, and mechanical compression due to trapped fluid in tissues (Gil et al., 2017).

The treatment of extravasation injuries that result from infiltration of medications and IV solutions is controversial. Many infiltrates resolve spontaneously following the removal of the IV catheter. Treatment involves the use of specific antidotes and may be based on the staging of the infiltrate. Three possible antidotes—hyaluronidase, phentolamine, and topical nitroglycerin paste—have been studied most extensively in the neonatal population. The mechanism by which IV fluids and medications cause tissue necrosis varies, and optimal treatment choices vary with each extravasated agent (Gil et al., 2017; Ramasethu, 2004; Thigpen, 2007; Table 21.5).

Intraosseous Administration

Intraosseous placement, medication administration directly into the marrow of a bone, may be a viable alternative for parenteral drug delivery in neonates. This route of administration may be considered when IV access cannot be readily obtained. Use of intraosseous access is widely accepted in the pediatric population during resuscitation efforts. A recent study examined the use of intraosseous medication administration as opposed to umbilical venous cannulation (UVC) in a simulated neonatal resuscitation in the delivery room. Intraosseous access was faster and was not perceived as more technically difficult in this simulated trial. Intraosseous medication administration may be a viable alternative to UVC placement in certain neonatal resuscitations (Rajani, Chitkara, Oehlert, & Halamek, 2011).

Intranasal Administration

Intranasal delivery allows use of the highly vascularized nasal mucosa and olfactory tissue to facilitate the rapid transport of specific medications into the bloodstream and brain. The onset of intranasal administration approaches that of parenteral medication delivery. In addition to the ease of administration, the fact that no needle stick is involved makes this an attractive medication delivery modality. Key factors to the intranasal administration of medications include the use of both nares to increase available surface area for drug absorption and the use of concentrated medications (Milesi et al., 2017; Wolfe & Braude, 2010).

TABLE 21.5

EXTRAVASATION TREATMENT

Extravasated Drug/Fluid	Treatment
Parenteral nutrition	Topical nitroglycerin, hyaluronidase
Calcium	Topical nitroglycerin, hyaluronidase
Dopamine	Phentolamine, topical nitroglycerin
Dobutamine	Phentolamine
Epinephrine	Phentolamine

Source: Adapted from Ramasethu, J. (2004). Pharmacology review: Prevention and management of extravasation injuries in neonates. *NeoReviews, 5,* 491–497. doi:10.1542/neo.5-11-e491

Aerosol Administration

The use of aerosolized medications in the neonatal setting has increased with the resurgence of bronchopulmonary dysplasia, the increased prevalence of pulmonary hypertension, and to assist in pharmacologic medication management in infants with no IV access. The rationale for aerosol medication delivery includes direct delivery to the target organ (lungs) with decreased systemic ADEs (Sahni & Phelps, 2011). An example of an aerosolized medication is prostacyclin for pulmonary hypertension treatment in neonates.

Overall, the therapeutic efficacy of aerosolized medications depends on the delivery of an adequate dose of medication to the target sites within the lung. The primary factors that influence lung deposition include particle size, mode of assisted ventilation, inhaler device and placement, and age of the infant. The available methods to aerosolize medications in the neonate include nebulization either intermittently or continuously or a metered-dose inhaler (MDI) with a spacing device. Studies have revealed conflicting results with regard to the optimal method and efficacy of aerosol drug delivery in the neonate, including systems for mechanically ventilated infants. Those infants on oscillatory ventilation present further unique medication delivery challenges (Mazela & Polin, 2011).

Medication Administration in Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation (ECMO) is a highly technical and invasive technique used to treat cardiorespiratory failure when conventional means and technologies fail. ECMO is used for a variety of indications in the neonatal population, including those with persistent pulmonary hypertension, meconium aspiration, sepsis, respiratory distress syndrome, pneumonia, congenital diaphragmatic hernia, and in postoperative congenital heart disease patients. Patients who undergo ECMO receive on average more than 10 different medications, including antibiotics, sedatives, analgesics, inotropes, diuretics, antiepileptics, and medications that are used to maintain the ECMO circuit. Varying pharmacokinetics may be observed, depending on the actual site of injection. There is substantial variability between individual circuits. In general, larger volumes of distribution and decreased drug clearance are observed.

Medications may be administered to ECMO patients either into the ECMO circuit before or after the filter or directly into the patient. Distribution and delivery of medication are more consistent when drugs are injected after the filter. Administration into this site places the patient at risk for development of air emboli, and administration of medications should be done with great caution. Medications injected directly into the reservoir or before the filter usually result in a prolonged time of actual drug delivery to the patient and incomplete drug administration. A large part of the ECMO circuit consists of disposable polyvinyl chloride or silicone tubing of varying length, oxygenators, and centrifugal pumps. The amounts of tubing and other components contribute to a large surface area with the potential for drug binding, particularly for highly lipophilic medications. Therefore, increased doses may be required initially when these medications are used or when the circuit is changed or primed with blood or crystalloid during ECMO therapy (Lonabaugh, Lunsford, Fang, & Kaufman, 2017; Wildschut, Allegaert, Ahsman, Mathot, & Tibboel, 2010).

Interpretation of pharmacokinetic parameters in this type of patient is often difficult because of the influences of the site of injection, flow rate of the ECMO circuit, and clinical status and organ function of the patient. Gentamicin and vancomycin are two antibiotics that are commonly administered to infants on ECMO. Pharmacokinetics for these agents vary, not only with the ECMO circuit but also with the clinical status of the infant—including altered renal function in a sick infant. In addition, pharmacokinetics was found to vary with the infant's GA, postnatal age, and weight. Peak effect for these patients is often delayed, thus resulting in false interpretation of serum peak levels for aminoglycoside antibiotics (Wildschut et al., 2010).

MEDICATION SHORTAGES

In 2011, the White House focused legislation to curb drug shortages of life-sustaining or supporting medications. Such medications are those whose discontinuation could have life-threatening consequences, including medications used to treat specific neonatal conditions. The focus of drug shortages also targets those drug companies that voluntarily choose to discontinue a medication, which then may lead to a national drug shortage. Companies are to notify the FDA 6 months in advance of their intent to discontinue production of such a medication.

Despite this legislation, the United States has experienced both an increased number and duration of medication shortages over the past decade. ISMP has noted that 6% of adverse outcomes with drug shortages occur when a pharmacy attempts to compound a strength of a medication that is no longer available (Lau, Khazanie, Rowe, & Fauman, 2016). This can be extremely problematic in the neonatal population.

The neonatal population has seen the impact of such national shortages over the past several years. Parenteral electrolytes including sodium, potassium, and calcium salts have led to restricted use of such agents based on availability. In addition, restrictions in parenteral nutrition solutions of essential trace macronutrients including pediatric amino acid formulations and multivitamins may have long-term consequences for the growth and development of infants. Some institutions find themselves with a shortage of parenteral vitamin K, an agent used routinely to prevent hemorrhagic disease of the newborn (Traynor, 2011; Ventola, 2011).

SUMMARY

The individualization of drug therapy is critical in the neonatal population. The neonatal population presents a unique challenge with regard to both medication dosing and administration. Drug dosing on a mg/kg basis is the most common method because of the ease of calculation. A lack of large, well-controlled trials in this unique patient population results in drug dosing based on extrapolation from the adult literature or anecdotal experience. Furthermore, developmental pharmacokinetics—or the change in ADME of drugs—creates a population whose drug dosing is constantly changing. Once an appropriate dosing regimen is determined, the optimal drug administration technique including smart infusion pumps as well as oral syringe devices with metric markings is equally important to avoid iatrogenic adverse medication events.

EVIDENCE-BASED PRACTICE BOX

Quality Improvement: Oral Glucose Gel for Neonatal Hypoglycemia

Neonatal hypoglycemia is a leading cause for admission to the neonatal intensive care unit (NICU) with current therapeutic options resulting in interruption of breastfeeding and mother–infant bonding. Low blood glucose levels are common among newborn infants with an estimated prevalence of 15% of newborns. As little as one low glucose level may contribute to problems with academic achievement and development during childhood. Infants on the first or second day of life may be asymptomatic or have symptoms including hypotonia, lethargy, jitteriness, seizures, hypothermia, congestive heart failure, or poor feeding.

Neonatal hypoglycemia should be treated as soon as possible to prevent complications of neurologic damage. Neonatal hypoglycemia is defined as a plasma glucose level of less than 30 mg/dL in the first 24 hours of life and less than 45 mg/dL thereafter.

New treatment algorithms use a more novel therapy, oral glucose 40% gel, extrapolated from adult experience. This allows treatment without the use of intravenous dextrose or interruption of breastfeeding. Dosing of 200 mg/kg/dose (or 0.5 mL/kg/dose) orally for one dose STAT is recommended at most centers (Bennett, Fagan, Chaharbakhsi, Zamifiirova, & Flicker, 2016). Some centers utilize this more novel therapeutic option only in neonates 35 weeks of gestation or greater (Harris, Weston, Signal, Chase, & Harding, 2013).

Storage of 40% dextrose gel tubes in automated dispensing cabinets in Labor and Delivery, Mother Baby Units, and NICUs provides options for rapid therapy. The opportunity for suppliers to manufacture a glucose gel product that is dye and preservative free in smaller unit of use packaging would be more appropriate for neonates. A significant decrease in admission rates to the NICU for hypoglycemia and supporting mother–infant bonding are two factors favoring this new therapeutic option.

References

Bennett, C., Fagan, E., Chaharbakhsi, E., Zamifiirova, M. S., & Flicker, B. A. (2016). Implementing a protocol using glucose gel to treat neonatal hypoglycemia, *Nursing for Women's Health*, *1*, 64–74. doi:10.1016/j.nwh.2015.11.001

Harris, D. L., Weston, P .J., Signal, M., Chase, J. G., & Harding, J. E. (2013). Dextrose gel for neonatal hypoglycemia (the Sugar Babies Study): A randomized double-blind, placebo-controlled trial. *Lancet, 382*(9910), 2077–2083. doi:10.1016/S0140-6736(13)61645-1

PARENT VOICES

Tracy Pella

We gave birth to our twins at 23 + 4 weeks. One of our sons passed away the same day and our other son spent 134 days in the NICU. While in the NICU, our son was on several medications. As a parent, this was very overwhelming. Doctors and nurses would explain the medication and the need for our son to have them. They would do their best to explain them in layman terms. On most days, we were told more information than we could process. Not only were we first-time parents, but neither of us came from a medical background. For the most part, providers were willing to explain. As a nurse, please remember many of us parents are highly educated and deeply care about our child's health, yet medical terms and medications may need to be explained in a way we are able to understand. Often, our questions may be taken as challenging, but they are truly to be able to fully understand what you need us to know.

ONLINE RESOURCES

Reiter, P. D. (2002). Neonatal pharmacology and pharmacokinetics. *NeoReviews, 3*(11), e229–e236. doi:10.1542/neo.3-11-e229

Segar, J. L., Dagle, J. M., Tierney, S. B. (n.d.). *Pharmacology: NICU handbook* (Online). Retrieved from https://uichildrens.org/health-library/pharmacology-nicu-handbook

REFERENCES

Allegaert, K., & van den Anker, J. N. (2014). Adverse drug reactions in neonates and infants: A population related approach is needed. *British Journal of Clinical Pharmacology, 80(4),* 788–795. doi:10.1111/bcp.12430

American Academy of Pediatrics. (2017). Weighing all patients in kilograms [Statement of endorsement]. *Pediatrics*, *140*(4), e20172476. doi:10.1542/peds.2017-2476

American Society of Health-System Pharmacists. (2016, October 25). *Standardize 4 Safety Initiative releases final IV recommendations for medication safety* [Press release]. Retrived from https://www.ashp.org/news/2016/10/25/standardize-4-safety-initiative-releases-final-iv-recommendations-for-medication-safety

Beall, V., Hall, B., Mulholland, J. T., & Gephart, S. M. (2013). Neonatal extravasation: An overview and algorithm for evidence-based treatment. *Newborn and Infant Nursing Reviews, 13*(4), 189–195. doi:10.1053/j.nainr.2013.09.001

Eidelman, A. I., Schanler, R. J., Johnston, M., Landers, S., Nobel, L., Szucs, K., & Viehmann, L. (2012). Breastfeeding and the use of human milk. *Pediatrics, 129*(3), e827–e841. doi:10.1542/peds.2011-3552

Engle, W. A., Blackmon, L. R., Batton, D. G., Bell, E. F., Denson, S. E., Kanto, W. P., Jr., . . . Stark, A. (2004). Age terminology during the perinatal period [Policy statement]. *Pediatrics, 114*(5), 1326–1364 (reaffirmed July 2014). doi:10.1542/peds.2004-1915

Food and Drug Administration. (2014, December 13). FDA issues final rule on changes to pregnancy and lactation labeling information for prescription drug and biological products. Retrieved from http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm425317.htm

Food and Drug Administration. (2017, April). Use of codeine and tramadol products in breastfeeding women. Retrieved from https://www/fda.gov/drugs/postmarket-drug safety-information-patients-and-providers/use-codeine-and-tramadol-products-breastfeeding-women-questions-and-answers

Fullas, F., Padomek, M. T., Thieman, C. J., & Van Gorp, A. E. (2011) Comparative evaluation of six extended-interval gentamicin dosing regimens in premature and full-term neonates. *American Journal of Health-System Pharmacy, 68*(1), 52–56. doi:10.2146/ajhp100114

Gil, J. A., Shah, K. N., Suarez, L., & Weiss, A. C. (2017). Upper-extremity extravasation: Evaluation, management, and prevention. *Journal of Bone and Joint Surgery, 5*(8), 1–9 doi:10.2106/JBJS.RVW.16.00102

Harding, A. (2011). Use of intravenous smart pumps for patient safety. *Journal of Emergency Nursing, 37*(1), 71–72. doi:10.1016/j.jen.2010.07.006

Institute for Safe Medication Practices. (2015). ENFit enteral devices are on their way . . . Important safety considerations for hospitals. Retrieved from http://www.ismp.org/newsletters/acutecare/showarticle.aspx?id=105

Institute for Safe Medication Practices. (2017). Targeted medication safety best practices for hospitals. Retrieved from https://www.ismp.org/guidelines/best-practices-hospitals

Institute for Safe Medication Practices & VON. (2017, December 27). *Standard concentrations of neonatal drug infusions*. Retrieved from https://www.ismp.org/Tools/PediatricConcentrations.pdf

Johnson, P. J. (2011). Neonatal pharmacology—pharmacokinetics. *Neonatal Network, 30*(1), 54–61. doi:10.1891/0730-0832.30.1.54

The Joint Commission. (2008, April 11). Preventing pediatric medication errors. *Sentinel Event Alert*, (39). Retrieved from http://www.jointcommission.org/assets/1/18/SEA_39.PDF

Kearns, G. L., Abdel-Rahman, S. M., Alander, S. W., Blowey, D. L., Leeder, J. S., & Kauffman, R. E. (2003). Developmental pharmacology—Drug disposition, action, and therapy in infants and children. *New England Journal of Medicine, 349*(12), 1157–1167. doi:10.1056/NEJMra035092

Krzyaniak, N. (2016). Review of drug utilization patterns in NICUs worldwide. *Journal of Clinical Pharmacy and Therapeutics*, *41*, 612–620. doi:10.1111/jcpt.12440

Krzyaniak, N., & Bajorek, B. (2016). Medication safety in neonatal care: A review of medication errors. *Therapeutic Advances in Drug Safety, 7*, 102–119. doi:10.1177/2042098616642231

Ku, L., & Smith, P. B. (2015). Dosing in neonates: Special considerations in physiology and trial design. *Pediatric Research, 77*, 2–9. doi:10.1038/pr.2014.143

Laforgia, N., Nuccio, M. M., Schettini, F., Dell'Aera, M., Gasbarro, A. R., Dell'Erba, A., & Solarino, B. (2014). Off-label and unlicensed drug use among neonatal intensive care units in Southern Italy. *Pediatrics International, 56*(1), 57–59. doi:10.1111/ped.12190

Lau, B., Khazanie, U., Rowe, E., & Fauman, K. (2016). How a drug shortage contributed to a medication error leading to baclofen toxicity in an infant. *The Journal of Pediatric Pharmacology and Therapeutics, 21*(6), 527–529, doi:10.5863/1551-6776-21.6.527

Lonabaugh, K. P., Lunsford, K. J., Fang, G. Y., & Kaufman, D. A. (2017). Vancomycin dosing in pediatric extracorporeal membrane oxygenation: Potential impacts of new technologies. *The Journal of Pediatric Pharmacology and Therapeutics, 22*(5), 358–363. doi:10.5863/1551-6776-22.5.358

Mazela, J., & Polin, R. (2011). Aerosol delivery to ventilated newborn infants: Historical challenges and new directions. *European Journal of Pediatrics, 170*(4), 433–444. doi:10.1007/s00431-010-1292-6

Mennella, J. A., & Beauchamp, G. K. (2008). Optimizing oral medications for children. *Clinical Therapeutics, 30*(11), 2120–2132. doi:10.1016/j.clinthera.2008.11.018

Milesi, C., Baleine, J., Mura, T., Benito-Castro, F., Ferragu, F., Thiriez, G., . . . Cambonie, G. (2017). Nasal midazolam vs ketamine for neonatal intubation in the delivery room: A randomised trial. *Archives of Disease in Childhood—Fetal and Neonatal Edition, 103*(3), F221–F226. doi:10.1136/archdischild-2017-312808

Monagle, P., Studdert, D. M., & Newall, F. (2011, June 17). Infant deaths due to heparin overdose: Time for a concerted action on prevention. *Journal of Pediatrics and Child Health, 48*(5), 380–381. doi:10.1111/j.1440-1754.2011.02127.x

Murphy, A. D., Gilmour, R. F., & Coombs, C. J. (2017). Extravasation injury in a pediatric population. *ANZ Journal of Surgery*, *89*(4), E122–E126. doi:10.1111/ans.14104

Neville, K. A., Frattarelli, D. A. C., Galinkin, J. L., Green, T. P., Johnson, T. D., Paul, I. M., & Van Den Anker, J. N. (2014). Off-label use of drugs in children [Policy statement]. *Pediatrics, 133*(3), 563–567. doi:10.1542/peds.2013-4060

O'Hara, K., Wright, I. M., & Schneider, J. J. (2015). Pharmacokinetics in neonatal prescribing, evidence base, paradigms and future. *British Journal of Clinical Pharmacology, 80*(6), 1281–1288. doi:10.1111/bcp.12741

Paul, I. M., Neville, K., Galinkin, J. L., Green, T. P., Johnson, T. D., Sullivan, J., & Van Den Anker, J. N. (2015). Metric units and the preferred dosing of orally administered liquid medications. *Pediatrics, 135*(4), 784-787. doi:10.1542/peds.2015-0072

Pernia, S., & DeMaagd, G. (2016). The new pregnancy and lactation labeling rule. *Pharmacy and Therapeutics, 41*(11), 713–715. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5083079

Phillips, M. S. (2011). Standardizing IV infusion concentrations: National survey results. *American Journal of Health-System Pharmacy, 68*(22), 2176–2882. doi:10.2146/ajhp110001.

Poole, R. L., & Carleton, B. C. (2008). Medication errors: Neonates, infants and children are the most vulnerable. *Journal of Pediatric Pharmacology and Therapeutics, 13*(2), 65–67. Retrieved from https://www.jppt.org/doi/abs/10.5863/1551-6776-13.2.65

Rajani, A., Chitkara, R., Oehlert, J., & Halamek, L. P. (2011). Comparison of umbilical venous and intraosseous access during simulated neonatal resuscitation. *Pediatrics, 128*(4), e954–e958. doi:10.1542/peds.2011-0657

Ramasethu, J. (2004). Pharmacology review: Prevention and management of extravasation injuries in neonates. *NeoReviews, 5*, 491–497. doi:10.1542/neo.5-11-e491

Ramoz, L. L, & Patel-Shori, N. M. (2014). Recent changes in pregnancy and lactation labeling: Retirement of risk categories. *Pharmacotherapy, 34(*4), 389–395. doi:10.1002/phar.1385

Reed, M. D. (2011). Reversing the myths obstructing the determination of optimal age- and disease-based drug dosing in pediatrics. *Journal of Pediatric Pharmacology and Therapeutics, 16*(1), 4–13. Retrieved from https://www.jppt.org/doi/abs/10.5863/1551-6776-16.1.4

Riley, M., & Meyers, R. (2016). Position statement on heparin safety concerns. *Journal of Pediatric Pharmacology and Therapeutics, 21*(6), 530–532. doi:10.5863/1551-6776-21.6.530

Rinke, M. L., Bundy, D. G., Velasquez, C. A., Rao, S., Zerhouni, Y., Lobner, K., . . . Miller, M. R. (2014). Interventions to reduce pediatric medication errors: A systematic review. *Pediatrics, 134*(2), 338–360. doi:10.1542/peds.2013-3531

Robertson, A. F. (2003a). Reflections on errors in neonatology II. The heroic years, 1950 to 1970. *Journal of Perinatology, 23*(2), 54–161. doi:10.1038/sj.jp.7210843

Robertson, A. F. (2003b). Reflections on errors in neonatology III. The experienced years, 1970 to 2000. *Journal of Perinatology, 23*(3), 240–249. doi:10.1038/sj.jp.7210873

Rostas, S. E. (2017). Medication safety in the neonatal intensive care unit: Big measures for our smallest patients. *The Journal of Perinatal & Neonatal Nursing, 31*, 15–19. doi:10.1097/JPN.0000000000000230

Rumore, M. M. (2016). Medication repurposing in pediatric patients: Teaching old dog new tricks. *Journal of Pediatric Pharmacology and Therapeutics, 21*(1), 36–53. doi:10.5863/1551-6776-21.1.36

Sahni, J., & Phelps, S. (2011). Nebulized furosemide in the treatment of bronchopulmonary dysplasia in preterm infants. *Journal of Pediatric Pharmacology and Therapeutics, 16*, 14–22. doi:10.1097/JPN.0000000000000230

Sauberan, J. B., Dean, L. M., Fiedelak, J., & Abraham, J. A. (2010). Origins and solutions for neonatal medication-dispensing errors. *American Journal of Health System Pharmacy, 67*(1), 49–57. doi:10.2146/ajhp090122

Shirkey, H. (1968). Therapeutic orphans. *Journal of Pediatrics, 72*, 119. doi:10.1016/S0022-3476(68)80414-7

Skog, J. (2016). ISO 80369 is coming—Will you be ready? *Tubing*, 34–37. Retrieved from https://www.mddionline.com/iso-80369-coming%E2%80%94will-you-be-ready

Soldin, O. P., & Soldin, S. J. (2002). Review: Therapeutic drug monitoring in pediatrics. *Therapeutic Drug Monitoring, 24*(1), 1–8. doi:10.1097/00007691-200202000-00001

Taketomo, C. K. (2017). *Pediatric and neonatal dosage handbook* (24th ed.). Hudson, OH: Lexi-Comp.

Taylor, J., McDonald, S., & Tan, K. (2015). Prevention of central venous catheter-related infection in the neonatal unit: A literature review. *The Journal of Maternal- Fetal and Neonatal Medicine*, *28*(10), 1224–1230. doi:10.3109/14767058.2014.949663

Thigpen, J. L. (2007). Peripheral intravenous extravasation: Nursing procedure for initial treatment. *Neonatal Network, 26*(6), 379–384.

Touw, D., Westerman, E., & Sprij, A. J. (2009). Therapeutic drug monitoring of aminoglycosides in neonates. *Clinical Pharmacokinetics, 48*(2), 71–88. doi:10.2165/00003088-200948020-00001

Traynor, K. (2011, December 1). White House addresses drug shortages. *American Society of Health System Pharmacists, 68*(23), 2204–2206. doi:10.2146/news110078

Trissel, L. A. (2016). Drug stability and compatibility issues in drug delivery. In L. A. Trissel (Ed.), *Handbook on injectable drugs* (19th ed.). Bethesda, MD: American Society of Health-System Pharmacists.

Ventola, C. L. (2011). The drug shortage crisis in the United States: Causes, impact, and management strategies. *Pharmacy and Therapeutics, 36*(11), 740–758. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3278171

Watterberg, K. L., Papile, L.-A., Adamkin, D. H., Baley, J. E., Bhutani, V. K., Carlo, W. A., . . . Wang, K. S. (2010). Postnatal corticosteroids to prevent or treat bronchopulmonary dysplasia [Policy statement]. *Pediatrics, 126*(4), 800–808 (reaffirmed January 2014). doi:10.1542/peds.2010-1534

Wharton, G. T. (2014). Impact of pediatric exclusivity on drug labeling and demonstrations of efficacy. *Pediatrics, 134*(2), e512–e518. doi:10.1542/peds.2013-2987

Wildschut, E. D., Allegaert, A. K., Ahsman, M. J., Mathot, R. A., & Tibboel, D. (2010). Determinants of drug absorption in different ECMO circuits. *Intensive Care Medicine, 36*(12), 2109–2116. doi:10.1007/s00134-010-2041-z

Wolfe, T. R., & Braude, D. A. (2010). Intranasal medication delivery for children: A brief review and update. *Pediatrics, 126*(3), 532–537. doi:10.1542/peds.2010-0616

Woo, T. M. (2004). Pediatric pharmacology update: Essential concepts for prescribing. *Advance Nursing Practice, 12*(6), 22–27. doi:10.1542/peds.2010-0616

Yin, H. S., Parker, R. M., Sanders, L. M., Mendelsohn, A., Dreyer, B. P., Bailey, S. C., ... Wolf, M. S. (2017). Pictograms, units and dosing tools and parent medication errors: A randomized study. *Pediatrics*, *140*(1), e201663237. doi:10.1542/peds.2016-3237

CHAPTER 22

Emerging Technologies in Neonatal Care: Healthcare Simulation for Neonatal Care

Carole Kenner

WHAT IS HEALTHCARE SIMULATION?

Over the past few years, the number of medical institutions opening healthcare simulation programs has increased exponentially (D. Arnold, LeMaster, Todd, & Wallin, 2012). The advent of advanced, high-fidelity simulation technology over the past 10 to 15 years has made this possible. Healthcare simulation is defined by David Gaba (2004) as, "a technique—not a technology—to replace or amplify real patient experiences with guided experiences, artificially contrived, that evoke or replicate substantial aspects of the real world in a fully interactive manner." Healthcare simulation involves four important components: (a) the scenario: the story where a participant is immersed in a realistic clinical situation; (b) the simulator: a tool used to create a realistic physical space, equipment, and/or patient such as a mannequin; (c) the experience: suspension of disbelief and "near-life" experience during the scenario by the participants; and (d) the debrief: reflective discussion where the learning occurs (see Figure 22.1).

Simulation in healthcare is an ever-evolving educational methodology that began over 20 years ago in the field of anesthesiology (Gaba, 1992; Rosen, 2008). It has taken a long time for the medical field to embrace simulation, likely due to the limitations of realistic simulators, but also due to the resistance in traditional medical education to try new methods of education, when tried and true methods such as lectures and bedside teaching have seemingly worked. However, simulation offers benefits that cannot be achieved in traditional lecture or bedside teaching with the mantra of *see one, do one, teach one* educational activities. It is based on adult learning principles, making it a very effective tool for educating healthcare providers (see Table 22.1; J. Arnold, 2011). Adult learners, including providers in neonatal care, are independent, self-directed, and motivated to learn when what they are learning applies to their professional roles (Murphy & Halamek, 2005). Adult learners also respond well to receiving immediate feedback on their performance and being able to apply their newly acquired knowledge right away. Additionally, simulation can provide education on demand with the opportunity to repeat high-risk situations until all participants manage a situation properly. Simulation bridges the gap between education and the acquisition of high-stakes, low-frequency skills in clinical practice that are essential for acquisition and maintenance of skills in high-risk patient care fields, such as neonatal intensive care (Galloway, 2009). It is being used for inpatient care as well as the transition home.

Most importantly, simulation is an educational opportunity where it is safe to make mistakes—there is no risk to patients. In fact, the goal of high-fidelity simulation encounters is often for participants to make mistakes. Every mistake made in a simulation is a mistake that could then be prevented in the real world. Previously, other high-risk industries such as aviation and nuclear power have utilized simulation to improve safety and minimize risk.

Simulation-based research in healthcare continues to show that use of simulation-based learning methodologies enhances performance in both real-life clinical situations and simulated resuscitations (Andreatta, Saxton, Thompson, & Annich, 2011). In addition, use of debriefings after real or simulated resuscitations have been found to result in improved learning, knowledge, and skills (Rudolph, Taylor, & Foldy, 2001). Some units are filming resuscitations for the purposes of improving teamwork, neonatal outcomes, and to debrief after the event. These films are destroyed after team reviews. Although these scenarios are not simulations, they are another example of the use of technology in neonatal training and quality improvement. This chapter outlines various technologies that are impacting neonatal care.

History of Healthcare Simulation

Simulation, although growing in use in healthcare education, has been used for many years in other high-risk industries. Military, aviation, and nuclear power have been using simulation to practice and prepare for rare and/or dangerous situations and highly strategic missions. Simulation in healthcare has learned many lessons from all these industries, especially the aviation industry. In the early years of aviation, simulation pilots practiced the technical skills of taking off, flying, and landing a plane as early as the time of the first planes and gliders. From the early days of gliding, it was usual for "pilots" to sit in the glider, which was exposed to a strong facing wind, and "feel" how to keep the wings horizontal with their controls (Moore, 2008). Flight simulation has now moved forward to highly advanced and realistic technology cockpit simulators that allow pilots to practice flight crises they hope they will never encounter in their careers. However, despite very realistic and advanced flight simulation training in which all pilots participated, up until the 1980s, the aviation industry was concerned about the frequency of major flight crises. So big was the problem that NASA launched an all-out study of jet transport accidents and incidents between 1968 and 1976 and found that the leading causes of these accidents were not deficiencies in the

FIGURE 22.1 Near-life experience in simulation.
Source: Courtesy of Texas Children's Hospital.

TABLE 22.1

HOW ADULT LEARNING PRINCIPLES CORRELATE WITH HEALTHCARE SIMULATION

Adult Learning Principle	Simulation Curriculum Correlate
Adults prefer to apply what they learn soon after learning it	Simulation provides immediate, hands-on practice
Adults prefer learning concepts and principles	Preparation and presentation of key concepts prior to simulation allows for conceptual learning
Adults learn better at their own pace	Simulation provides repetitive and deliberate practice educational opportunities
Adults like to help set their own learning objectives	Learner-focused debriefings after simulation allow for reflection on personal objectives
Adults like to receive immediate feedback	Debriefing, enhanced with video review of simulation scenarios, is real time, immediate, and learner focused

Source: Adapted from Arnold, D., LeMaster, T., Todd, F., & Wallin, K. (2012, January 27). *Hospital-based simulation programs: Sharing operational models, practices, and strategies.* Abstract presentation at The International Meeting for Simulation in Healthcare, San Diego, CA.

pilot's knowledge or skill, but, more likely, failures in teamwork, communication, and leadership (Cooper, White, & Lauber, 1980). With this information, aviation developed a new form of training, coined Crew Resource Management, which focused on training the whole aircraft team on human factors such as effective communication, flat hierarchy, teamwork, workload distribution, and situational awareness (Helmreich & Sexton, 2003; Helmreich, Wilhelm, Klinect, & Merritt, 2001). As a result of the initiation of Crew Resource Management in aviation in the 1980s, it is much safer to fly our blue skies.

Healthcare simulation has evolved from the lessons learned in aviation simulation. Although healthcare simulation began as early as the 1960s with the development of the first low-fidelity mannequin-based simulator, Resusci Anne® by Laerdal, as a field, simulation in healthcare has had a rapid surge in activity, technological advances, and research over the past 10 years. Resusci Anne, a low-fidelity or low-tech mannequin, was developed and introduced in 1960 by Norwegian toymaker Asmund S. Laerdal (Laerdal Medical Company, 2012). He teamed up with two physicians, anesthesiologist Peter Safar, MD, and emergency medicine physician James Elam, MD, who developed mouth-to-mouth breathing (the airway component of CPR), as a life-saving procedure. Together, they developed a life-sized doll to train medical and nonmedical personnel in CPR. Resusci Anne was modeled after a young girl whose body was pulled from the River Seine in Paris at the turn of the 19th century. Her death was a popular story in Europe at the time. It was assumed she had committed suicide over unrequited love, by jumping in the river, as there were no other visible causes of death. Because her identity could not be established, a death mask was made as was customary at the time. Moved by her story, Asmund S. Laerdal adopted her mask for the face of his new resuscitation-training mannequin.

Healthcare simulation has come a long way since Resusci Anne. We now have everything from virtual reality and haptic simulators to whole-body mannequins that are so realistic and interactive that healthcare providers forget a mannequin-based patient is not real. Whole-body, highly technical mannequins are often referred to as high-fidelity mannequin-based simulators. These mannequins are so sophisticated that they have pulses and breathe, have heart and lung sounds, turn blue when cyanotic, talk or cry, sweat or bleed, and sometimes move (Figures 22.2 and 22.3). In neonatal simulation, there are four high-fidelity, whole-body mannequins now available (Table 22.2). Each has slightly different features; therefore, the choice of the best simulator is based on the needs of the specific simulation scenario one is trying to create. Some of the Laerdal mannequins today are being used to teach Helping Babies Breathe,® a low technology resuscitation program for low-resource countries as well as the breastfeeding mannequin to teach breastfeeding techniques. Both these mannequins are of low technology but serve the same purpose as the high-fidelity simulations—to gain skills without patient risk.

The high-fidelity mannequins take this training to another level. They interact with the providers. When a healthcare team administers a drug or an intervention, the mannequin's vital signs

FIGURE 22.2 High-fidelity mannequin-based simulators.
Source: Courtesy of Texas Children's Hospital.

FIGURE 22.3 Sophisticated mannequin in neonatal simulation.
Source: Courtesy of Texas Children's Hospital.

can change appropriately. Now, a healthcare team is able to take care of a patient in a realistic environment in real time without the interruptions of a teacher telling them the vitals or asking what they might do in that situation. Now, the team must actively do all the things needed to appropriately care for their patient in a safe environment.

Simulation and Patient Safety

Simulation is an increasingly recognized tool to improve patient safety in healthcare. It provides an effective method to meet the needs of adult learners, while improving patient safety and outcomes through a safe environment, to improve and maintain skill proficiency.

Medical error accounts for approximately $24 billion in healthcare costs annually in the United States and 98,000 lives lost annually. It is the fifth leading cause of death in the United States. Both the Institute of Medicine (IOM) and The Joint Commission (TJC) have reported that medical errors result from deficiencies in teamwork, leadership, and communication rather than technical or cognitive deficiencies, similar to that of the aviation industry (TJC, 1998; Kohn, Corrigan, & Molla, 2000). In 1999, the IOM's *To Err Is Human: Building a Safer Healthcare System* found that the leading causes of medicine errors (70%) were due to lack of communication and leadership, not a lack of medical knowledge or skill of the practitioner (Laerdal Medical Company, 2012). Similarly in 2004 and 2007, the TJC during extensive review of sentinel events found lack of teamwork, communication, and safety culture as the leading cause of error in these events. The TJC has recommended that all healthcare institutions implement simulation-based training to improve teamwork and communication. Just as the aviation industry developed Crew Resource Management to address deficiencies in teamwork, leadership, and communication, healthcare has developed Crisis Resource Management (CRM) training. CRM in healthcare simulation was first described by David Gaba, MD, an anesthesiologist and the father of modern healthcare simulation (Rall & Gaba, 2005). He reported 15 important CRM skills, such as role clarity, effective communication, personnel support, adequate use of all resources, and situational awareness, that all effective healthcare teams should embody to deliver safe care during high-risk clinical situations. Because simulation-based training focuses more on behavioral and teamwork skills than on individual technical skills, it provides the perfect opportunity for multidisciplinary teams to train together and practice these skills. Up until now, healthcare professionals have trained in silos: nurses in nursing school, physicians in medical school, and so on. However, when a patient crashes, healthcare providers are expected to work as a well-oiled team to successfully resuscitate a patient, even though they may have never had an opportunity to practice working together. In today's complex healthcare system, healthcare needs pit crews, not cowboys. No longer are autonomy, knowledge and experience, and self-sufficiency enough to provide safe and effective healthcare. Now, more than ever, healthcare providers need to work as a team within a system to provide safe and effective care. High-fidelity simulation provides opportunity for healthcare teams to only practice these important skills in a time-pressured, realistic, and safe environment.

There is a growing body of evidence that not only technical skills but also behavioral skills are improved with simulation-based training, ultimately improving patient care outcomes and decreasing medical errors (Andreatta et al., 2006, 2011; Barsuk, Cohen, Feinglass, McGaghie, & Wayne, 2009). In obstetrics and gynecology, researchers have shown that team-based simulation training can result in decreased need for massive transfusion protocols in postpartum hemorrhage situations (Lockhart, Allen, Gunatilake, Hobbs, & Taekman, 2012). Additionally, units conducting simulation-based training on management of shoulder dystocia have shown improved neonatal Apgar scores, decreased incidence of brachial plexus injuries in newborns, and decreased incidence of neonatal hypoxic–ischemic encephalopathy (Draycott et al., 2008). Simulation-based team training has shown improved collaboration between obstetrics and neonatology (Zabari et al., 2006). In our field of neonatology, simulation-based training has shown increased success rates in neonatal intubations after simulation training (Arnold et al., 2008), but there is a need for additional research to show the impact of simulation-based training in neonatal patient outcomes.

Simulation in Neonatal Care

Simulation provides an opportunity to practice high-risk patient care situations so that providers are more competent in their abilities to manage these situations. Because neonatal intensive care involves unexpected high-risk clinical situations, simulation is a tool to improve patient care outcomes.

Simulation-based training in neonatal care had its beginning in the Neonatal Resuscitation Program (NRP; Halamek et al., 2000; Murphy & Halamek, 2005). With studies showing that cognitive and technical skills achieved are typically retained for only 6 to 12 months, the goal of implementation of a simulation-based training curriculum was to improve learning and skills of healthcare providers caring for newborns requiring resuscitation at the time of delivery (Kaczorowski et al., 1998). It is not only recommended by national and international organizations including the International Liaison Committee on Resuscitation that oversee implementation of the NRP, but since its sixth edition, simulation-based training is now required (Perlman et al., 2010). In the seventh edition (Weiner, Zaichkin, & Kattwinkel, 2016),

TABLE 22.2

EXAMPLES OF HIGH-FIDELITY NEONATAL MANNEQUIN-BASED SIMULATORS

Features	SimNewB (Laerdal Medical)	Newborn Hal (Gaumard Scientific)	Premie Hal (Gaumard Scientific)	PEDI Blue Neonatal Simulator (Nasco)
Airway/ breathing	Realistic airway, normal and abnormal breath sounds, bilateral and unilateral chest rise, CO_2 exhalation	Realistic airway, normal and abnormal breath sounds, bilateral and unilateral chest rise	Realistic airway, normal and abnormal breath sounds, bilateral and unilateral chest rise	Realistic airway, bilateral chest rise
Cyanosis	Central, pulse oximetry	Central, pulse oximetry	Central, pulse oximetry	Peripheral and central
Circulation/EKG	Normal and abnormal heart sounds, central and peripheral pulses, EKG monitoring	Normal and abnormal heart sounds, central and peripheral pulses, EKG monitoring	Normal and abnormal heart sounds, central and peripheral pulses, EKG monitoring	None
Movement	All extremities: limp, tone, motion, seizure	Upper extremities: limp, tone, motion, seizure	None	None
Vocal sounds	Cry, grunt, stridor, cough, hiccup	Cry, grunt, stridor	Cry, grunt, stridor	None
Access procedures	Patent umbilical vein and arteries with blood flashback, bilateral intraosseous access	Patent umbilical vein with blood flashback, peripheral IV, bilateral intraosseous access	Patent umbilical vein with blood flashback, peripheral IV, bilateral intraosseous	Patent umbilical vein
Airway procedures	BVM, intubation, LMA, needle thoracentesis	BVM, intubation, LMA	BVM, intubation, LMA	BVM, intubation
Control	Wireless hand-held or tethered laptop	Wireless tablet PC	Wireless tablet PC	Tethered computer panel
Cost	$$$	$$$	$$$	$
Other	Interchangeable pupils, blood pressure	Gastric distention, bowel sounds, blood pressure	Premature newborn at 28 weeks	

BVM, bag-mask ventilation; IV, intravenous; LMA, laryngeal mask airway.

it does include simulated cases that are offered online. The incorporation of simulation-based methodology addresses the complex behavioral skills, such as effective teamwork and communication, that are essential in the resuscitation of the newborn. The NRP instructors are required to have the knowledge and skills needed to conduct simulation-based training: how to design simulation scenarios and debrief using reflective questions. Although the NRP has been a leader in embracing simulation since early on, it is only the beginning for the many potential uses and benefits in neonatal care.

There is a growing body of evidence that not only technical skills but also behavioral skills are improved with simulation-based training, ultimately improving patient care outcomes and decreasing medical errors (Andreatta et al., 2006, 2011; Barsuk et al., 2009; Draycott et al., 2008; Zabari et al., 2006). In the care of newborns, simulation-based training has been shown to improve provider success rates at endotracheal intubation, decreased incidence of hypoxic–ischemic encephalopathy, and improvement in Apgar scores (J. Arnold et al., 2008; Draycott et al., 2008).

Implementation of Simulation in Neonatal Care

The first step in the development of simulation-based neonatal activity is to determine the purpose of simulation activity. Five major categories in simulation can be used to help describe the purpose of simulation activity: (a) education, (b) competency and assessment, (c) research and development, (d) quality and patient safety, and (e) advocacy. Although simulation is an educational tool, it can be utilized for very different purposes beyond education. As a neonatal care provider is exploring and developing simulation training opportunities, it is vital to determine the purpose of the initiative in order to develop a useful and successful simulation initiative.

Simulation for Educational Purposes. Using simulations to provide training to meet the educational demands of neonatal

healthcare providers is the first category and most common use of simulation. Simulation-based education and training is primarily focused on delivering new knowledge/skills and/or providing practice and instruction to improve the learners' performance in a simulated event. It is important that all simulation-based educational activities are based on sound educational principles. (Please see the section Simulation for Competency and Assessment on simulation scenario design for key steps in this process.)

Simulation for Competency and Assessment. The goal of using simulation for assessment of skills and competency is growing. There is a need for development of validated simulation scenarios and assessment tools using validated and reliable measurement principles. Simulation has been shown to be helpful in demonstrating and evaluating competency in nursing training programs, advanced cardiac life support, advanced and emergency airway management, pediatric code resuscitation, CRM skills, laparoscopic surgical skills, and even bronchoscopy (Anderson, Murphy, Boyle, Yaeger, & Halamek, 2006; Calhoun, Rider, Meyer, Lamiani, & Truog, 2009; Konge, Arendrup, von Buchwald, & Ringsted, 2011; Lucisano & Talbot, 2012; Lutrell, Lenburg, Scherubel, Jacob, & Koch, 1999; Vaillancourt et al., 2011; Wayne et al., 2007).

Task trainers such as intubation trainers (Laedral), Lumbar Injection Simulators (3B Scientific, Tucker, Georgia), micro-preemie training baby simulator by Anatomy Warehouse (Evanston, IL), and Gaumard's (Miami, FL) PEDI® Blue Newborn Simulator offering CPR training and debriefing are just a few of the neonatal products available.

In anesthesia and surgical fields, simulation is an accepted means for maintenance of certification for physicians. Currently, other certifying bodies already utilize simulation in their certification processes such as the Medical Council of Canada, U.K. General Medical Council, National Board of Osteopathic Medical Examiners, and the U.S. Medical Licensing Examination (TJC, 2010). The disciplines within neonatology who are most advanced in adoption of simulation to assess competency and skills are neonatal nurses and advanced practitioners or neonatal nurse practitioners (NNPs; Cates & Wilson, 2011). National Certification Corporation (NCC), which offers certification for neonatal nurses, now has a module called *Simulation Enhancing Nursing Education & Practice* available for purchase (NCC, 2018).

Simulation Research and Development. There is a need to foster and develop research and quality improvement studies to advance the science of healthcare simulation (Issenberg, McGaghie, Petrusa, Lee Gordon, & Scalese, 2005). If possible, all simulation-based activities should have measurable and publishable outcomes. Needed areas of research include, but are not limited to:

1. Identification of which debriefing techniques and adjuncts best enhance learning
2. Identification of the optimal simulation educational approach based on the level of learner, skill of the faculty, and specific learning objectives
3. Development of "best practices" for simulation training in healthcare
4. Procedural or technical skills simulation research such as:
   a. Number of times needed for practice of a skill before competence is achieved
   b. Duration of time before procedural skills deteriorate
   c. Training in technical skills in simulation extrapolate to improve performance in skill on patients
   d. Validation of task trainers, virtual reality, and computer-based simulators
   e. Simulation training to decrease time from novice to expert
5. Use of simulation methodology as an assessment tool of technical and behavioral skills in healthcare providers
   a. Determination of the number and content of simulations required to assure an acceptable level of reliability
   b. Development and validation of reproducible scenarios with reliable and valid assessment tools for evaluating professional competence for the purpose of promotion, certification, or licensure
6. Development of reliable reproducible simulation-based scenarios for use across multiple institutions
7. Effects of fatigue on healthcare performance: team behaviors, decision making, communication skills, and error rates

Simulation for Quality and Patient Safety. Ultimately, all healthcare simulation activities have the potential to improve quality and patient safety. The best way to achieve this is to align simulation-based activities with national, local, and institutional patient safety and quality goals and needs. By qualitative research design and measurement, changes in patient care outcomes can be tracked and reported. Examples of this type of simulation include, but are not limited to:

1. In situ simulation to identify potential latent threats to patient safety in the clinical setting
2. Evaluation and testing of new hospital environments, technologies, equipment, or processes before being utilized in real patient care
3. Recreation of near misses and serious safety events to help identify causes and prevent future events

Advocacy in Simulation. Using simulation as a tool for advocacy for patient care is broad. It involves supporting the larger community with simulation-based activities. This can include:

1. Promoting simulation at a national or local level through media and public relations opportunities so that laypersons understand and might support healthcare simulation
2. Lobbying for healthcare legislature to support funding for healthcare simulation
3. Providing simulation-based education to laypersons, such as parents, so that they are better prepared to care for medical emergencies and crises at home or out of hospital

SCENARIO DEVELOPMENT

Just as in other more traditional curricular development models, simulation scenario design must be standardized and evidence based. It is important to realize that development of simulation educational events should be based on learning objectives and not on the features of mannequins or technology. Effective simulation scenario is essentially one where the learning objectives are achieved. Second, by incorporating real-life cases into scenarios, it not only improves the credibility of the cases for learners, but learners are also able to manage clinical problems and situations as they would in real-world practice. A series of steps are required to develop an effective and evidence-based scenario. For example, if one wanted to develop a scenario for educational purposes with the goal of training a healthcare team in how to manage a neonatal code, the process might look like this:

Step 1: Identification of the Purpose of the Scenario

Typically, when designing a scenario, it is recommended that the first step be to identify the purpose of the simulation: education, training, competency/assessment, research, or to address a patient

safety goal. Once you know the goal of the simulation session, it is easy to write learning objectives and determine a clinical case that can be created to meet the desired goal. In this case, the goal would be educational in nature.

Step 2: Identification of the Learning Objectives

The learning objectives should be determined based on the goal of the scenario. It is helpful to categorize learning objectives by their type: cognitive, technical, and behavioral. Although many simulation scenarios provide an opportunity to address many learning objectives, it is helpful to narrow the scope of the scenario to three or four at most so that the learners are able to synthesize these objectives.

Step 3: Identification of the Learners/ Participants

It is important to identify who will be the participants. Will it be a single or multidisciplinary team? How many learners per group? For this scenario, a learner group might consist of two neonatal nurses, one neonatal physician, one NNP, and one neonatal respiratory therapist. In general, the number of learners per simulation should reflect the appropriate number and type of providers for the clinical case.

Step 4: Identification of a Clinical Case to Create in Order to Achieve the Desired Learning Objectives

A patient clinical scenario should be developed that will allow the learning objectives to be met. The clinical situation must be realistic and appropriate to the level of the learners. For example, one might not want to choose management of congenital diaphragmatic hernia for a group of new nurses or residents; rather, a case of neonatal shock may be better aligned with their level of expertise. In this example case, one might choose a case of Group B streptococcal septic shock to address the needed learning objectives.

Step 5: Completion of a Scenario Design Template

Many simulation programs have developed and tailored their own simulation scenario design templates. Certain important pieces of information must be known ahead of time in order to conduct an effective simulation. Most simulation education instructors utilize a scenario design template or script that identifies all the necessary equipment and technology needed, the learners, the roles of instructors, the room setup, the expected scenario flow (a script like a play or movie), the appropriate mannequin physiological states based on actions of the learners, and the expected actions of the learners during a simulation. It is also very important to base the scenario and debriefing on the most recent evidence so that the educational experience is evidence based.

Step 6: Development of Debriefing Script Based on Learning Objectives

Although many topics discussed during the debriefing after a simulation scenario will be based on the performance and actions of the participants, it is important to keep the debriefing focused on the learning objectives. Time during a debriefing is limited, and although many teachable points will be raised during a simulation scenario, it is important to prioritize the discussion to the planned learning objectives. Therefore, it is often helpful to plan ahead with a few open-ended questions that will address the learning objectives. Some educators develop very detailed scripted debriefing questions to address these topics.

Step 7: Practice and Rehearsal of the Scenario

Every time a simulation scenario is run, the participants will likely act and perform differently. Therefore, it is very important to practice a scenario so that the scenario developers can ensure that the appropriate cues are available and that the learning objectives are achieved. When conducting a dress rehearsal, one often identifies medical equipment or auditory and visual cues that may be missing in order for the learners to be able to share the same mental model of the case as you intended.

Step 8: Implementation and Evaluation of the Simulation Scenario

As with any educational intervention, it is important to continuously re-evaluate the effectiveness of the intervention. Getting feedback from learners and instructors is important so that simulation scenarios can be continuously refined and improved.

NEONATAL APPS

A newer area of neonatal technology is the apps. These range from interactive drug calculators to apps that offer algorithms or infographics for common neonatal conditions, neonatal checklists to guide health professionals, and parent support apps such as those found at Support 4 NICU Parents (http://support4nicuparents.org/apps-for-nicu-parents). All of these apps are aimed at use of technology to support professionals and parents in providing care in the hospital and at home.

VIRTUAL CONSULTATIONS

Use of telemedicine is growing with neonatal specialists-physicians and nurses reaching out to provide consultations to community-based hospitals. These consults may be for assessments or for diagnostic reasons. They may be used to determine whether a baby needs to be transferred to a tertiary center or can remain in the birth hospital. Some of the early adopters of this technology are Arkansas Children's Hospital, Little Rock, Arkansas; Nationwide Children's, Columbus, Ohio; Children's Medical Center, Dallas; and Fauquier Hospital in Virginia. Telemedicine is being used after discharge to keep the babies in their homes with fewer hospital appointments (Robinson, Gund, Sjoqvist, & Bry, 2016).

SUMMARY

Simulation is a highly effective and innovative educational tool. It can be used for many purposes, including healthcare education, quality improvement, and patient safety. Although simulation can be a resource-intensive endeavor, when utilized appropriately, it can greatly improve healthcare provider performance and patient care outcomes. Simulation provides a mechanism for bringing the healthcare team together—students or practicing professionals to learn and practice the art of working together in a safe environment. This is another way that patient safety and quality will be improved through simulated interprofessional experiences. Use of technologies, whether through apps or virtual consults, is growing as is the evidence to support skill development/maintenance as well as impact on neonatal/family outcomes.

CASE STUDY

A sample of a simulation scenario in neonatal resuscitation.

Learning Objectives of the Scenario. By the end of the simulation session, learners should be able to:

- Cognitive
  1. Recognize the signs and symptoms of meconium aspiration syndrome in a neonate
  2. Develop a differential diagnosis of respiratory distress in a neonate
  3. Identify appropriate initial resuscitation and management steps in a newborn with meconium aspiration
- Technical
  1. Provide appropriate airway management skills for the neonate with meconium aspiration:
     a. Supplemental oxygen
     b. Tracheal intubation
     c. Positive-pressure ventilation
     d. Surfactant replacement
     e. Inhaled nitrous oxide
  2. Obtain umbilical venous and arterial access
  3. Provide intravenous (IV) fluid resuscitation and dextrose as indicated
- Behavioral
  1. Utilize appropriate teamwork and communication skills during a neonatal resuscitation, including:
     a. Identification of a team leader and other team roles
     b. Appropriate utilization of resources
     c. Effective communication, including closed-loop communication

Background for Learners of the Problem. This is a case of a newborn born with meconium aspiration syndrome who is to be managed by the NICU team following initial resuscitation.

■ Assessment: History and Physical Examination

History

- Baby girl is a 3,800-g estimated 38-week female born to a 16-year-old G1P1 with good prenatal care
- Maternal prenatal labs: mother: O+/− HIV—RPR pending HbsAg−, UDS: positive for marijuana
- Mother presented to L&D with loss of fluid approximately 24 hours prior to presentation, at 10 cm and +5 station
- Infant was born via precipitous spontaneous vaginal delivery with thick, foul-smelling meconium and fetal decels
- Mother developed fever to 102 at presentation
- At delivery, no spontaneous respirations noted, infant taken to warmer and suctioned below cords ×2 with return of thick meconium and started on bag-mask ventilation for 30 seconds with spontaneous respirations noted
- Heart rate was greater than 100 throughout resuscitation
- Peripheral IV placed at L&D and started on 40% oxygen via facemask with continuous positive airway pressure (CPAP) for desaturation and increased work of breathing
- Patient brought to NICU immediately without further intervention for initiation of respiratory support and prolonged rupture of membranes with chorioamnionitis; Apgar scores were 61, 85

■ Physical Examination Upon Presentation to NICU

- GENERAL: pale with thready pulses, poor peripheral perfusion
- VITAL SIGNS: baseline vital signs
- Temperature 98.3, HR 180, RR 78, BP 45/38, O_2 85% on 40% Fio_2 on FM with CPAP 8
- HEENT: AFOF, small caput, ears normal, palate intact, eyes open, pupils reactive to light; positive red reflex and normal facies
- RESP: lung fields bilaterally with coarse crackles and severe intracostal, subcostal, and substernal retractions noted; gasping respiratory effort on CPAP
- CV: rate regular with small II/VI systolic ejection murmur noted; poor peripheral perfusion, capillary blood refill time greater than 5 seconds, and thready pulses
- ABD: abdomen soft and nontender with no hepatosplenomegaly or masses; three-vessel cord; anus patent
- GENITOURINARY: normal female infant genitalia
- NEURO: decreased responses and tone
- EXTREMITIES: normal
- SKIN: pale with poor perfusion and mildly cyanotic; pronounced circumoral and acrocyanosis; no rashes or lesions

■ Differential Diagnoses

- Meconium aspiration syndrome
- Perinatal hypoxic–ischemic injury
- Shock
- Disseminated intravascular coagulation
- Sepsis
- Congenital cardiac defect

■ Diagnostic Tests

Laboratory Tests:

- CBC/differential: WBC 20.3, segmented cells 44; bands 30; hematocrit (Hct) 48%, platelet count 168,000/mm^3
- Glucose: 68
- Baby blood type and Coombs: baby: O+/−

Imaging Tests:

- Chest x-ray: bilaterally hazy with patchy areas of consolidation and atelectasis, hyperinflated to 10 ribs bilaterally, cardiac silhouette within normal limits

■ Simulation Scenario Setup and Logistics

Room Configuration (Setup). NICU inpatient room, infant warmer with neonatal high-fidelity mannequin on bed, covered up, no monitors on. Scenario starts with arrival of baby on CPAP from the labor and delivery room with transport team with portable warmer/isolette. Labor and delivery neonatal resuscitation team calls NICU when leaving L&D with brief handoff of patient to allow NICU team time to set up.

■ Equipment Needed

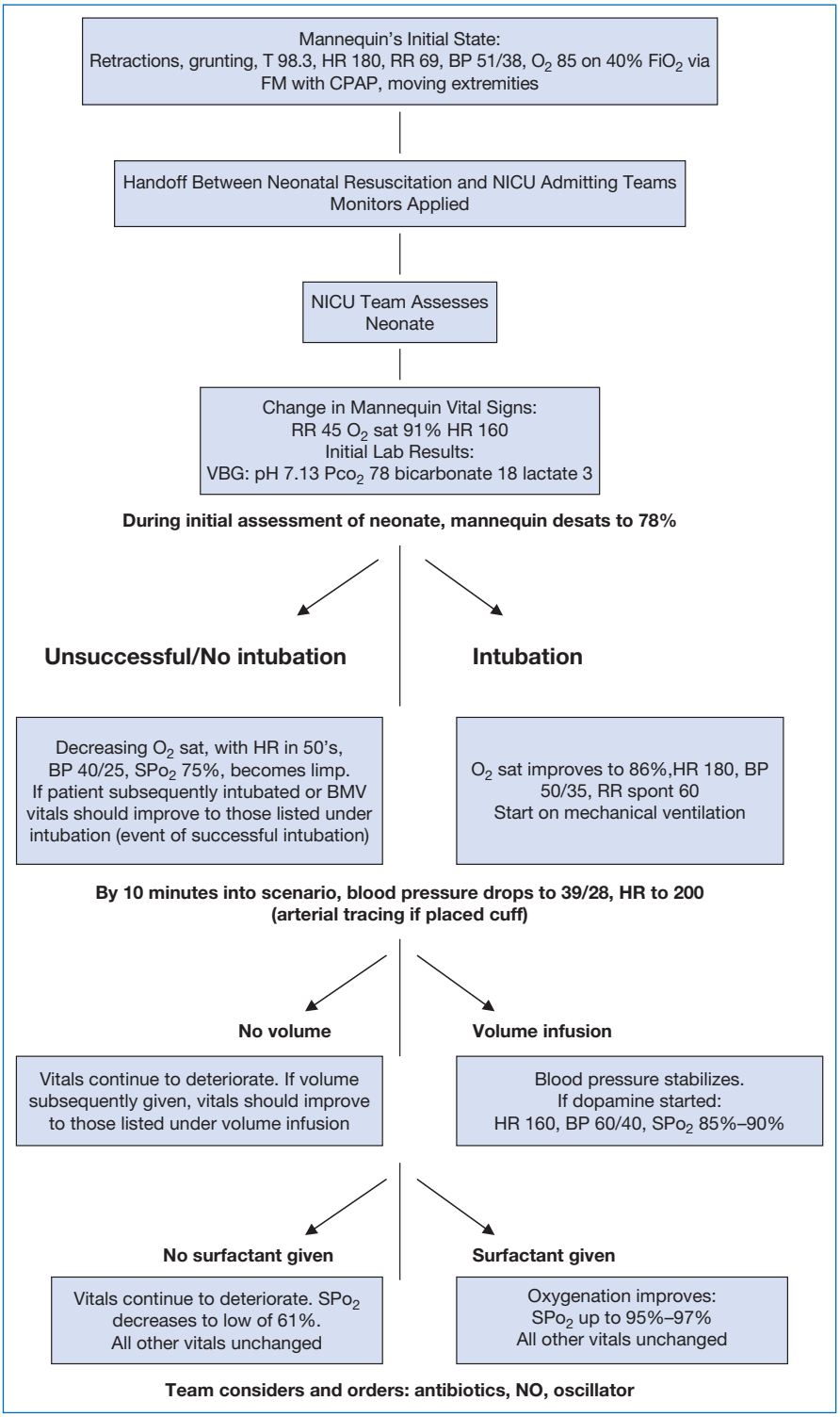
- High-fidelity neonatal mannequin with thick green moulage
- CPAP
- Ventilator (conventional and oscillator)
- Central-line access kit (umbilical)
- Neonatal crash cart
- Neonatal "fake" medications
- Airway supplies, including bag-mask and intubation equipment

■ Mannequins/Task Trainers/Confederates Needed

- High-fidelity neonatal mannequin: mannequin on admitting bed with a diaper and a hat only and some dark green thick moulage; peripheral intravenous (PIV) in place, CPAP on mannequin
- Low-fidelity neonatal mannequin: mannequin with hat and diaper on in transport isolette, attached to CPAP and Fio_2 at 40%, PIV in place
- Neonatal resuscitation team (confederate roles)
- Neonatal resuscitation team shows up with transport warmer/isolette with low-fidelity neonatal mannequin inside to start the scenario with a handoff to NICU admitting team.

■ Simulation Scenario Flow (Flow Chart)

Expected Scenario Flow. Neonatal resuscitation team (confederate team) arrives to bedside with transport warmer/isolette (low-fidelity



BMV, bag mask valve; BP, blood pressure; CPAP, continuous positive airway pressure; FiO_2, fraction of inhaled oxygen; FM, facial mask; HR, heart rate; NICU, neonatal intensive care unit; NO, nitric oxide; O_2, oxygen; RR, respiratory rate; T, temperature; VBG, venous blood gases.

mannequin), and report is given to NICU admitting team (learner team); transport team relays important information and background of neonate's course and history in the delivery room. After handoff to the admitting NICU team, the high-fidelity mannequin should be exposed (blanket removed), and the team should provide care to their new patient. The neonate should be placed on monitors. All appropriate providers should be in the room (nurses, physicians, respiratory therapists). The team should manage their patient until stabilized or 20 minutes of time has elapsed.

Expected Interventions of the Participants. The patient should be placed on monitors and vital signs assessed. Respiratory distress should be addressed first with noninvasive, then invasive ventilatory techniques. Recognition of possible meconium aspiration and sepsis should occur. The infant should be intubated and surfactant ordered. A chest x-ray should be obtained. Central access should be obtained, with appropriate labs sent and antibiotics ordered. Hypotension should be recognized and treated first with fluid resuscitation, then consider pressors. Failure of conventional ventilation should be recognized, and the team should consider inducible nitric oxide (iNO) and oscillator. The scenario ends when the following are achieved:

- Intubation
- Central-line access
- Fluid resuscitation
- Ordering and/or administration of surfactant, antibiotics, maintenance in vitro fertilization, iNO, and inotropes

Mannequin Operation: Scenario Flow Based on Participants' Interventions and Time

Debriefing. At the completion of the scenario, the instructor should lead a facilitative, reflective discussion of the learner's performance during the simulation. Concepts of a safe and confidential learning environment should be reinforced. The debriefing should focus on the learning objectives and issues that arose during the simulation such as things done well or not as well as desired by the team, questions the learners have based on the scenario, or other items of interest to the learners or the instructor. If possible, the debriefing should use video review of the scenario during the discussion. A typical debriefing lasts two to three times the duration of the simulation.

EVIDENCE-BASED PRACTICE BOX

Healthcare simulation is defined by David Gaba as "a technique—not a technology—to replace or amplify real patient experiences with guided experiences, artificially contrived, that evoke or replicate substantial aspects of the real world in a fully interactive manner" (Gaba, 2004). Healthcare simulation involves four important components: (a) the scenario: the story where a participant is immersed in a realistic clinical situation; (b) the simulator: a tool used to create a realistic physical space, equipment, and/or patient such as a mannequin; (c) the experience: suspension of disbelief and "near-life" experience during the scenario by the participants; and (d) the debrief: reflective discussion where the learning occurs.

Simulation is an educational opportunity where it is safe to make mistakes—there is no risk to patients. In fact, the goal of high-fidelity simulation encounters is often for participants to make mistakes. Simulation is an increasingly recognized tool to improve patient safety in healthcare. It provides an effective method to meet the needs of adult learners, while improving patient safety and outcomes through a safe environment, to improve and maintain skill proficiency. There is a growing body of evidence that clinician performance and patient care outcomes are improved with simulation-based training, ultimately improving patient care outcomes and decreasing medical errors (Andreatta et al., 2006; Andreatta, Saxton, Thompson, & Annich, 2011; Barsuk, Cohen, Feinglass, McGaghie, & Wayne, 2009). In obstetrics and gynecology, researchers have shown that team-based simulation training can result in decreased need for massive transfusion protocols in postpartum hemorrhage situations (Lockhart, Allen, Gunatilake, Hobbs, & Taekman, 2012). Additionally, units conducting simulation-based training on management of shoulder dystocia have shown improved neonatal Apgar scores, decreased incidence of brachial plexus injuries in newborns, and decreased incidence of neonatal hypoxic–ischemic encephalopathy (Draycott et al., 2008). Simulation-based team training has shown improved collaboration between obstetrics and neonatology (Zabari et al., 2006). Simulation-based training in newborn resuscitation has shown increased success rates in neonatal intubations after simulation training (Arnold et al., 2008), but there is a need for additional research to show the impact of simulation-based training in neonatal patient outcomes.

When developing and implementing simulation-based education, just as in other more traditional curricular development models, simulation scenario design must be standardized and evidence based. It is important to realize that development of simulation educational events should be based on learning objectives and not the features of mannequins or technology. An effective simulation scenario is essentially one in which the learning objectives are achieved. A series of steps are required to develop an effective and evidence-based scenario. It is important that all simulation instructors receive formal training in how to implement and debrief simulation scenarios. Debriefing is a challenge, and most literature supports the need for educators to be trained in effective debriefing principles. Debriefing requires learner self-reflection and facilitative feedback in a psychologically safe environment (Rudolph, Simon, Dufresne, & Raemer, 2006; Rudolph, Simon, Raemer, & Eppich, 2008). An educator must take time to develop an evidence-based scenario and practice before implementation to ensure that learning objectives are achieved. Simulation is a highly effective and innovative educational tool. It can be used for many purposes, including healthcare education, quality improvement, and patient safety. Although simulation can be a resource-intensive endeavor, when utilized appropriately, it can greatly improve healthcare provider performance and patient care outcomes.

References

Andreatta, P., Saxton, E., Thompson, M., & Annich, G. (2011). Simulation-based mock codes significantly correlate with improved pediatric patient cardiopulmonary arrest survival rates. *Pediatric Critical Care Medicine, 12*(1), 33–38. doi:10.1097/PCC.0b013e3181e89270

(*continued*)

EVIDENCE-BASED PRACTICE BOX (*continued*)

Andreatta, P. B., Woodrum, D. T., Birkmeyer, J. D., Yellamanchilli, R. K., Gerard, M., Doherty, G. M., . . . Minter, R. (2006). Laparoscopic skills are improved with LapMentor training: Results of a randomized, double-blinded study. *Annals of Surgery, 243*(6), 854–860. doi:10.1097/01.sla.0000219641.79092.e5

Arnold, J., Hamilton, F., Kloesz, J., Clark, R., Kanter, S., Lowmaster, B., . . . Kochanek, P. (2008, May 2). *Effect of a high fidelity simulation curriculum on pediatric resident competency in neonatal airway management skills*. Pediatric Academic Societies Meeting, Honolulu, HI.

Barsuk, J. H., Cohen, E. R., Feinglass, J., McGaghie, W. C., & Wayne, D. B. (2009). Use of simulation-based education to reduce catheter-related bloodstream infections. *Archives of Internal Medicine, 169*(15), 1420–1423. doi:10.1001/archinternmed.2009.215

Draycott, T. J., Crofts, J. F., Ash, J. P., Wilson, L. V., Yard, E., Sibanda, T., & Whitelaw, A. (2008). Improving neonatal outcome through practical shoulder dystocia training. *Obstetrics and Gynecology, 112*(1), 14–20. doi:10.1097/AOG.0b013e31817bbc61

Gaba, D. (2004). *Crisis management in anesthesiology* (2nd ed.). New York, NY: Churchill Livingstone.

Lockhart, E., Allen, T., Gunatilake, R., Hobbs, G., & Taekman, J. (2012, January 27). *Use of human simulation for the development of a multidisciplinary obstetric massive transfusion protocol*. International Meeting for Simulation in Healthcare, San Diego, CA.

Rudolph, J. W., Simon, R., Dufresne, R. L., & Raemer, D. B. (2006). There's no such thing as a 'nonjudgmental' debriefing: A theory and method for debriefing with good judgment. *Simulation in Healthcare, 1*, 49–55. doi:10.1097/01266021-200600110-00006

Rudolph, J. W., Simon, R., Raemer, D. B., & Eppich, W. (2008). Debriefing as formative assessment: Closing performance gaps in medical attention. *Academic Emergency Medicine, 15*, 1110Y–1116Y. doi:10.1111/j.1553-2712.2008.00248.x

Zabari, M., Suresh, G., Tomlinson, M., Lavin, J. P., Jr., Larison, K., Halamek, L., & Schriefer, J. A. (2006). Implementation and case-study results of potentially better practices for collaboration between obstetrics and neonatology to achieve improved perinatal outcomes. *Pediatrics, 118*(Suppl. 2), S153–S158. doi:10.1542/peds.2006-0913m

ONLINE RESOURCES

Boston Children's Hospital Simulator Program. Retrieved from http://simpeds.org/center_of_excellence/sim-neonatology

Center for Advanced Pediatric & Perinatal Education. A New Vision for Pediatric and Perinatal Education. Retrieved from http://cape.lpch.org

Children's Hospital of Philadelphia Resuscitation Education and Simulation. Retrieved from https://www.chop.edu/pediatric-residency-program/resuscitation-education-and-simulation

ECMOSim. Retrieved from http://cape.stanford.edu/programs/for-healthcare-providers/ecmosim-.html

NeoSim. Retrieved from http://cape.stanford.edu/programs/for-healthcare-providers/neosim-.html

Sawyer, T., Sierocka-Castaneda, A., Chan, D., Berg, B., Lustik, M., & Thompson, M. (2011). Deliberate practice using simulation improves neonatal resuscitation performance. *Simulation in Healthcare, 6*(6), 327–336. doi:10.1097/SIH.0b013e31822b1307

SimNewB®. Retrieved from http://www.laerdal.com/us/doc/88/SimNewB

Turning Technologies. (2012). *Clinical simulation to improve critical thinking in the neonatal intensive care–Dr. Jose Rojas* [Video file]. Retrieved from http://www.youtube.com/watch?v=Mf-RLRrc4XI

USW GlamorganUniversity. (2011). *Joy James teaces neonatal resuscitation skills in the clinical simulation centre* [Video file]. Retrieved from http://www.youtube.com/watch?v=TWaZBcjmxu8

REFERENCES

Anderson, J. M., Murphy, A. A., Boyle, B. B., Yaeger, K. A., & Halamek, L. P. (2006). Simulating extracorporeal membrane oxygenation (ECMO) emergencies. Part II: Qualitative and quantitative assessment and validation. *Simulation in Healthcare, 1*, 228–232. doi:10.1097/01.SIH.0000243551.01521.74

Andreatta, P., Saxton, E., Thompson, M., & Annich, G. (2011). Simulation-based mock codes significantly correlate with improved pediatric patient cardiopulmonary arrest survival rates. *Pediatric Critical Care Medicine, 12*(1), 33–38. doi:10.1097/PCC.0b013e3181e89270

Andreatta, P. B., Woodrum, D. T., Birkmeyer, J. D., Yellamanchilli, R. K., Gerard, M., Doherty, G. M., . . . Minter, R. (2006). Laparoscopic skills are improved with LapMentor training: Results of a randomized, double-blinded study. *Annals of Surgery, 243*(6), 854–860. doi:10.1097/01.sla.0000219641.79092.e5

Arnold, D., LeMaster, T., Todd, F., & Wallin, K. (2012, January 27). *Hospital-based simulation programs: Sharing operational models, practices, and strategies*. Abstract presentation at The International Meeting for Simulation in Healthcare, San Diego, CA.

Arnold, J. (2011). The neonatal resuscitation program comes of age. *Journal of Pediatrics, 159*(3), 357–358.el. doi:10.1016/j.jpeds.2011.05.053

Arnold, J., Hamilton, F., Kloesz, J., Clark, R., Kanter, S., Lowmaster, B., . . . Kochanek, P. (2008, May 2). *Effect of a high fidelity simulation curriculum on pediatric resident competency in neonatal airway management skills*. Pediatric Academic Societies Meeting, Honolulu, HI.

Barsuk, J. H., Cohen, E. R., Feinglass, J., McGaghie, W. C., & Wayne, D. B. (2009). Use of simulation-based education to reduce catheter-related bloodstream infections. *Archives of Internal Medicine, 169*(15), 1420–1423. doi:10.1001/archinternmed.2009.215

Calhoun, A. W., Rider, E. A., Meyer, E. C., Lamiani, G. E., & Truog, R. D. (2009). Assessment of communication skills and self-appraisal in the simulated environment: Feasibility of multirater feedback with gap analysis. *Simulation in Healthcare, 4*, 22–29. doi:10.1097/SIH.0b013e318184377a

Cates, L. A., & Wilson, D. (2011). Acquisition and maintenance of competencies through simulation for neonatal nurse practitioners. *Advances in Neonatal Care, 11*(5), 1–7. doi:10.1097/ANC.0b013e31822a34a0

Cooper, G. E., White, M. D., & Lauber, J. K. (Eds.). (1980). *Resource management on the flightdeck: Proceedings of a NASA/Industry workshop (NASA CP –2120)*. Moffett Field, CA: NASA-Ames Research Center.

Draycott, T. J., Crofts, J. F., Ash, J. P., Wilson, L. V., Yard, E., Sibanda, T., & Whitelaw, A. (2008). Improving neonatal outcome through practical shoulder dystocia training. *Obstetrics and Gynecology, 112*(1), 14–20. doi:10.1097/AOG.0b013e31817bbc61

Gaba, D. M. (1992). Improving anesthesiologists' performance by simulating reality. *Anesthesiology, 76*, 491–494. doi:10.1097/00000542-199204000-00001

Gaba, D. M. (2004). *Crisis management in anesthesiology* (2nd ed.). New York, NY: Churchill Livingstone.

Galloway, S. J. (2009). Simulation techniques to bridge the gap between healthcare professionals. *Online Journal of Issues in Nursing, 14*(2), manuscript 3. doi:10.3912/OJIN.Vol14No02Man03

Halamek, L. P., Kaegi, D. M., Gaba, D. M., Sowb, Y. A., Smith, B. C., Smith, B. E., & Howard, S. K. (2000). Time for a new paradigm in pediatric medical education: Teaching neonatal resuscitation in a simulated delivery room environment. *Pediatrics, 106*(4), e45–e53. doi:10.1542/peds.106.4.e45

Helmreich, R. L., & Sexton, B. J. (2003). *Analyzing cockpit communication: The links between language, performance, and workload*. Austin: The University of Texas, Department of Psychology.

Helmreich, R. L., Wilhelm, J. A., Klinect, J. R., & Merritt, A. C. (2001). *Culture, error and crew resource management*. Austin: The University of Texas, Department of Psychology.

Issenberg, S. B., McGaghie, W. C., Petrusa, E. R., Lee Gordon, D., & Scalese, R. J. (2005). Features and uses of high-fidelity medical simulations that lead to effective learning: A BEME systematic review. *Medical Teacher, 27*, 10–28. doi:10.1080/01421590500046924

The Joint Commission. (1998). *Sentinel events: Evaluating cause and planning improvement* (2nd ed.). Oakbrook Terrace, IL: Author.

The Joint Commission. (2010). Joint commission standard frequently asked questions. Retrieved from https://www.jointcommission.org/

Kaczorowski, J., Levitt, C., Hammond, M., Outerbridge, E., Grad, R., Rothman, A., & Graves, L. (1998). Retention of neonatal resuscitation skills and knowledge: A randomized controlled trial. *Family Medicine, 30*, 705–711.

Kohn, L. T., Corrigan, J. M., & Molla, S. D. (Eds.). (2000). *To err is human: Building a safer health system* (1st ed.). Washington, DC: National Academy Press.

Konge, L., Arendrup, H., von Buchwald, C., & Ringsted, C. (2011). Using performance in multiple simulated scenarios to assess bronchoscopy skills. *Respiration, 81*(6), 483–490. doi:10.1159/000324452

Laerdal Medical Company. (2012). The girl from the River Seine. Retrieved from http://www.laerdal.com/us/doc/367/History

Lockhart, E., Allen, T., Gunatilake, R., Hobbs, G., & Taekman, J. (2012, January 27). *Use of human simulation for the development of a multidisciplinary obstetric massive transfusion protocol*. International Meeting for Simulation in Healthcare, San Diego, CA.

Lucisano, K. E., & Talbot, L. A. (2012). Simulation training for advanced airway management for anesthesia and other healthcare providers: A systematic review. *AANA Journal, 8*(1), 25–31. Retrieved from https://cms.aana.com/docs/default-source/aana-journal-web-documents-1/simulationtraining_0212_p25-31.pdf?sfvrsn=44ad48b1_6

Lutrell, M., Lenburg, C., Scherubel, J., Jacob, S., & Koch, R. (1999). Competency outcomes for learning and performance assessment: Redesigning a BSN curriculum. *Nursing and Health Care Perspectives, 20*, 134–141.

Moore, K. (2008). A brief history of aircraft flight simulation. *Aircraft Flight Simulator*. Retrieved from https://www.simulationinformation.com/education/early-history-flight-simulation

Murphy, A. A., & Halamek, L. P. (2005). Simulation-based training in neonatal resuscitation. *NeoReviews, 8*, e489–e492. doi:10.1542/neo.6-11-e489

National Certification Corporation. (2018, November 10). WB2003 Simulation enhancing nursing education & practice. Retrieved from https://www.nccwebsite.org/Course/Detail/635

Perlman, J. M., Wyllie, J., Kattwinkel, J., Atkins, D. L., Chameides, L., Goldsmith, J. P., . . . Velaphi, S. (2010). Neonatal resuscitation: 2010 international consensus on cardiopulmonary resuscitation and emergency cardiovasular care science with treatment recommendations. *Pediatrics, 126*, e1319–e1344. doi:10.1542/peds.2010-2972B

Rall, M., & Gaba, D. (2005). Human performance and patient safety. In R. Miller (Ed.), *Miller's anesthesia* (pp. 3021–3072). Philadelphia, PA: Elsevier Churchill Livingstone.

Robinson, C., Gund, A., Sjoqvist, B-A., & Bry, K. (2016). Using telemedicine in the care of newborn infants after discharge from a neonatal intensive care unit reduced the need of hospital visits. *Acta Paediatrica, 105*(8), 902–909. doi:10.1111/apa.13407

Rosen, K. R. (2008). History of medical simulation. *Journal of Critical Care, 23*, 157–166. doi:10.1016/j.jcrc.2007.12.004

Rudolph, J. W., Taylor, S. S., & Foldy, E. G. (2001). Collaborative off-line reflection: A way to develop skill in action science and action inquiry. In P. Reason & H. Bradbury (Eds.), *Handbook of action research* (pp. 405–412). Thousand Oaks, CA: Sage.

Vaillancourt, M., Ghaderi, I., Kaneva, P., Vassiliou, M., Kolozsvari, N., George, I., . . . Feldman, L. S. (2011). GOALS—incisional hernia: A valid assessment of simulation laparoscopic hernia repairs. *Surgical Innovations, 18*(1), 48–54. doi:10.1177/1553350610389826

Wayne, D. B., Didwania, A., Feinglass, J., Fudala, M. J., Barsuk, J. H., & McGaghie, W. C. (2007). Simulation-based education improves quality of care during cardiac arrest team responses at an academic teaching hospital: A case-control study. *Chest, 133*(1), 56–61. doi:10.1378/chest.07-0131

Weiner, G. M, Zaichkin, J., & Kattwinkel, J. (2016). *Textbook of neonatal resuscitation* (7th ed.). Elk Grove Village, IL: American Academy of Pediatrics.

Zabari, M., Suresh, G., Tomlinson, M., Lavin, J. P., Jr., Larison, K., Halamek, L., & Schriefer, J. A. (2006). Implementation and case-study results of potentially better practices for collaboration between obstetrics and neonatology to achieve improved perinatal outcomes. *Pediatrics, 118*(Suppl. 2), S153–S158. doi:10.1542/peds.2006-0913m

CHAPTER 23

Pain in the Newborn and Infant

Marlene Walden and Carol Turnage Spruill

INTRODUCTION

Despite advances in neonatal pain assessment and management, nonpharmacologic and pharmacologic analgesic therapies continue to be underutilized to manage both acute and procedural pain (Carbajal et al., 2008; Committee on Fetus and Newborn and Section on Anesthesiology and Pain Medicine, 2016; Simons, van Dijk, Anand, et al., 2003). Untreated acute, recurrent, or chronic pain related to disease or medical care may have significant and lifelong physiologic and psychological consequences. As with all other medical conditions, the first step in the treatment process is the accurate diagnosis of the problem. Thus, pain assessment provides the foundation for all pain treatment. This chapter reviews the developmental neurophysiology of pain, discusses methods to assess pain in infants, highlights factors that influence the pain experience, and discusses evidence-based strategies for managing infant pain.

DEFINING PAIN IN INFANTS

Pain is defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" (Merskey, 1979). The IASP definition also states that pain is always subjective and is learned through experiences related to injury in early life. This definition is problematic when considering infants who are incapable of self-report and who may not have had previous experience with injury. Anand and Craig (1996) proposed that pain perception is an inherent quality of life that appears early in development to serve as a signaling system for tissue damage. This signaling includes behavioral and physiologic responses, which are valid indicators of pain that can be inferred by others. Broadening the definition of pain to include behavioral and physiologic indicators, in addition to self-report, can benefit preverbal, nonverbal, or cognitively impaired individuals who are experiencing pain by providing objective pain assessment.

More recently, researchers have attempted to develop uniform definitions of prolonged, persistent, or chronic pain in the newborn (Anand, 2017). In a Delphi study conducted by van Ganzewinkel and colleagues, chronic pain in the newborn is characterized by pain that is not proximate to a procedure or event, occurs over a period of time, has no clear endpoint in sight, and often is not associated with a specific cause (van Ganzewinkel, Anand, Kramer, & Andriessen, 2014). Furthermore, an acute painful event may alter pain perception where subsequent non-noxious events are perceived as painful. Signs and symptoms may be nonspecific, further hindering the ability of caregivers to accurately assess chronic pain in the neonate (van Ganzewinkel et al., 2014).

Risk factors for pain along with a high index of suspicion should be used in determining whether an infant is in pain and is in need of appropriate pain-relieving treatment. The primary tenet is that pain in the newborn should be presumed in all situations usually considered to cause pain in adults and children, even in the absence of behavioral or physiologic signs (Agency for Health Care Policy and Research, 1992; National Association of Neonatal Nurses, 2012).

DEVELOPMENTAL NEUROPHYSIOLOGY OF PAIN

The basic mechanisms of pain perception in infants and children are similar to those of adults and include (1) transduction and transmission and (2) perception and modulation. However, because of neurophysiologic and cognitive immaturity, some differences exist. A brief review is presented here and emphasizes the developmental and maturational changes that occur during infancy and childhood (Fitzgerald & Howard, 2003).

Peripheral Transduction and Transmission

Noxious mechanical, thermal, or chemical stimuli excite primary afferent fibers that transmit information about the potentially injurious stimuli from the periphery to the dorsal horn of the spinal cord. A-delta (large, myelinated, and fast-conducting) and C (small, unmyelinated, and slow-conducting) fibers are primarily responsible for pain impulse transmission (nociception). However, these signals can be amplified or attenuated by activation of surrounding neurons in the periphery and spinal cord. For example, tissue injury causes the release of inflammatory mediators (e.g., potassium, bradykinin, prostaglandins, cytokines, nerve growth factors, catecholamines, substance P) that sensitize A-delta and C fibers and recruit other neurons (silent nociceptors) and result in hyperalgesia. Stimulation of A-beta fibers that signal nonpainful touch and pressure can compete with the transmission of nociception in the dorsal horn of the spinal cord, thus reducing the intensity of the perceived pain.

Central Mechanisms and Modulation

Neurotransmitters in the spinal cord either amplify (e.g., substance P, calcitonin gene-related peptide, neurokinin A) or attenuate (e.g., endogenous opioids, norepinephrine, serotonin, GABA [gamma-aminobutyric acid], glycine) pain information from the periphery. Central sensitization occurs when excitatory amino acids act on NMDA (*N-methyl-D-aspartate*) receptors to induce prolonged depolarization and windup.

Nociceptive sensory input reaches the thalamus through second-order neurons in the spinothalamic, spinoreticular, and spinomesencephalic tracts and is then widely distributed throughout the brain. The perception, emotional interpretation, and cognitive meaning of nociceptive stimuli occur within a distributive neuromatrix; no one "pain center" exists. The sensory-discriminative, affective-motivational, and evaluative dimensions of pain perception are mediated by past experience and the context of the painful event. For example, nociceptive stimuli activate areas of the limbic system thought to control emotion, particularly anxiety. Thus, differences in physiologic, biochemical, and psychologic factors influence the perception of pain, making it an individual phenomenon.

Descending modulation occurs when efferent projections from supraspinal areas such as the periaqueductal gray, raphe nucleus, and locus coeruleus release inhibitory neurotransmitters. The major neurotransmitters that mediate descending inhibition are norepinephrine, serotonin, endogenous opioids, GABA, and acetylcholine.

Neurodevelopment of Pain Perception

Infants, even prematurely born infants, have the neurologic capacity to perceive pain at birth (Fitzgerald & Howard, 2003; Simons & Tibboel, 2006; Walker, 2013). The peripheral and central structures necessary for nociception are present and functional early in gestation (between the first and second trimesters). Functional maturation of the fetal cerebral cortex has been demonstrated by (1) near-infrared spectroscopy and electroencephalogram (EEG) patterns that demonstrate alterations in cortical evoked potentials, (2) measurement of cerebral glucose use that shows maximal metabolic rates in sensory areas of the brain, and (3) well-defined periods of sleep and wakefulness that are regulated by cortical functioning from 28 weeks' gestation. The newborn infant possesses a well-developed hypothalamic–pituitary–adrenal axis and can mount a fight-or-flight response with the release of catecholamines and cortisol.

Research suggests that some differences in nociceptive processes between infants and adults exist. For example, pain impulse transmission in neonates occurs primarily along nonmyelinated C fibers rather than myelinated A-delta fibers. The peripheral and central nervous systems in the preterm are also immature, leading to lower thresholds for activation, excitation, and transmission of nociceptive stimuli. Furthermore, the dorsal horn neurons in the spinal cord have large, overlapping cutaneous receptive fields that, when stimulated, amplify nociceptive signaling and can evoke long-term excitability within the spinal cord (Anand, 2017). Descending inhibitory neurotransmitters are also lacking, leading to decreased modulation of pain in the preterm neonate (Fitzgerald & Howard, 2003). Thus, young infants may perceive pain more intensely than do older children or adults because their descending control mechanisms are immature and thus limit their ability to modulate the experience.

Long-Term Consequences of Pain

Although pain can serve as a warning of injury, the effects of pain are generally deleterious. Pain evokes negative physiologic, metabolic, and behavioral responses in infants. These responses include autonomic instability, pulmonary dysfunction, and hormonal stress (Goldschneider & Anand, 2003). Pain and stress contribute to an increased allostatic load of preterm neonates in the neonatal intensive care unit (NICU). *Allostatic load* is the resulting wear and tear on the body from repeatedly adapting to adverse situations (Grunau, Holsti, & Peters, 2006). Painful procedures may result in heightened pain sensitivity to routine handling as well as delayed recovery from noxious and routine caregiving procedures.

Learning about pain occurs with the first pain experience and may have effects on subsequent pain perception and responses. Memory of pain in infants is evident from differences in responses to painful vaccination in infants who had undergone unanesthetized circumcision in comparison with infants who were uncircumcised or who received analgesia during circumcision (Taddio, Goldbach, Ipp, Stevens, & Koren, 1995; Taddio, Katz, Ilersich, & Koren, 1997).

Research has suggested that pain syndromes may be related to early pain experiences. Grunau, Whitfield, and Petrie (1994) reported that parents judged their former extremely-low-birth-weight (ELBW) infants at 18 months to be less sensitive to pain and have higher somatization (pain of unknown cause) compared with parents of full-term infants. On the contrary, other research has failed to demonstrate differences in somatization of former ELBW infants at age 9 years (Whitfield, Grunau, & Holsti, 1997) or at ages 17 to 19 years (Grunau, Whitfield, & Fay, 2004). Further research is needed to learn about pain and its effects in infancy and beyond.

CLINICAL ASSESSMENT OF PAIN

Presently, no easily administered, widely accepted, uniform technique exists for assessing pain in infants (Duhn & Medves, 2004). Current pain methods have several limitations. First, most pain instruments were developed for neonates undergoing acute procedural pain such as heel sticks and may not accurately capture pain in neonates with persistent, prolonged, or chronic pain. Pain instruments also require caregivers to subjectively assess behavioral responses of the neonate to pain, which may result in interobserver variability and limit consistent pain assessments. Furthermore, behavioral pain responses may be absent or elusive in critically ill neonates who are pharmacologically paralyzed for medical treatment, infants at end of life (EOL), or in infants with neurologic impairments (Hall & Anand, 2014). While future directions in pain assessment may include technologies such as the use of near-infrared spectroscopy, heart rate variability, or palmar skin conductance, this specialized equipment may not be readily available at the bedside (Hall & Anand, 2014; Mele, 2018).

A multidimensional pain assessment tool that includes measurements for both physiologic and behavioral indicators of pain is preferable given the multifaceted nature of pain (National Association of Neonatal Nurses, 2012; Walden, 2001). Selection of an appropriate clinical pain assessment method should be based first on the developmental age of the infant and second on the type of pain experienced (e.g., for procedural pain or postoperative pain). Published validity and reliability should be considered when choosing a pain assessment tool.

Multidimensional Pain Tools

The most commonly used published multidimensional infant-specific pain assessment tools with psychometric data are listed in Table 23.1. The Premature Infant Pain Profile (PIPP), originally developed in 1996, has been demonstrated in numerous studies to be a valid and reliable measure of acute pain in

TABLE 23.1

MOST COMMONLY USED MULTIDIMENSIONAL PAIN ASSESSMENT TOOLS IN NEWBORNS

Pain Instrument	Population	Indicators	Forms of Validity	Reliability Data
Premature infant pain profile (Stevens et al., 1996, 2010)	Preterm and term neonates from 28 to 40 weeks	Gestational age Behavioral state Heart rate Oxygen saturation Brow bulge Eye squeeze Nasolabial furrow	Face Content Construct	Inter- and intrarater reliability >0.93
CRIES: Neonatal Postoperative Pain Assessment Score (Bildner & Krechel, 1996)	Neonates from 32 to 60 weeks	**C**rying **R**equires oxygen to maintain saturation 95% **I**ncreased blood pressure and heart rate **E**xpression **S**leep state	Face Content Discriminant Concurrent (r = 0.49–0.73)	Interrater reliability >0.72
Neonatal Infant Pain Scale (Lawrence et al., 1993)	Preterm and term neonates	Facial expression Cry Breathing patterns Arm movement Leg movement State of arousal	Face Construct Concurrent validity (r = 0.53–0.84)	Interrater reliability >0.92
Neonatal Pain Agitation and Sedation Scale (Hummel, Puchalski, Creech, & Weiss, 2008)	Preterm and term neonates	Crying/irritability Behavior/state Facial expression Extremities/tone Vital signs	Concurrent Discriminate	Interrater reliability >0.90

infants (Stevens, Johnston, Petryshen, & Taddio, 1996; Stevens, Johnston, Taddio, Gibbins, & Yamada, 2010). The PIPP was revised (PIPP-R) in 2014 to enhance validity and feasibility (Stevens et al., 2014). The PIPP has been tested in neonates ranging in ages from extremely preterm up to 40 weeks' postconceptional age. The PIPP incorporates two contextual factors that may account for the infant's less robust pain responses that may result from their immaturity or behavioral state. By scoring infants who are younger or those who are asleep higher on the PIPP, the adjusted scores do not penalize infants who are known to be less capable of mounting a robust response to noxious stimuli. The PIPP contains two physiologic indicators (i.e., heart rate and oxygen saturation) and three facial indicators (i.e., brow bulge, eye squeeze, and nasolabial furrow). While total scores vary between 18 and 21 depending on the infant's gestational age, scores between 7 and 12 usually signify mild to moderate pain requiring nonpharmacologic pain relief measures and scores greater than 12 indicate moderate to severe pain requiring pharmacologic pain intervention in addition to comfort measures.

The CRIES was originally developed to assess postoperative pain in infants between 32 and 60 weeks' gestational age (Krechel & Bildner, 1995), but studies have also documented its clinical utility in assessing procedural pain in preterm and term neonates (Ahn, 2006; Belda, Pallas, De la Cruz, & Tejada, 2004; Herrington, Olomu, & Geller, 2004). The CRIES is an acronym for the five parameters it measures: **C**rying, **R**equires oxygen to maintain saturation greater than 95%, **I**ncreased vital signs, **E**xpression, and **S**leepless. Total scores for the CRIES range from 0 to 10, with scores less than 4 indicative of mild pain requiring nonpharmacologic pain relief measures and scores greater than or equal to 5 consistent with moderate to severe pain requiring pharmacologic intervention in conjunction with comfort measures.

The Neonatal Infant Pain Scale (NIPS) was originally developed to assess procedural pain in preterm and term newborns (Lawrence et al., 1993), but studies also validate its utility with postoperative pain (Rouss, Gerber, Albisetti, Hug, & Bernet, 2007; Suraseranivongse et al., 2006). The NIPS examines five behavioral parameters (i.e., facial expression, crying, arms, legs, and state of arousal) and one physiologic parameter (i.e., breathing pattern). Total score ranges from 0 to 7. While the researchers of the NIPS do not provide guidelines for pain interventions on the basis of total score, all pain instruments in neonates are based on the premise of increasing pain intensity. Therefore, in tools without scoring guidelines for pain management, when pain scores reach the midrange of the total possible points for that tool (i.e., ~4 or greater with the NIPS), the clinician may infer that the infant is experiencing moderate to severe pain and pharmacologic intervention for that pain is warranted.

The Neonatal Pain Agitation and Sedation Scale (N-PASS), developed by Hummel et al. (2008), is a five-item scale that measures both pain/agitation and sedation in preterm and term neonates with prolonged pain postoperatively and during mechanical

ventilation. The N-PASS examines four behavioral items (crying/irritability, behavior state, facial expression, extremities/tone) and one physiologic indicator (vital signs). Total pain scores range from 0 to +10. Like the PIPP, the N-PASS includes gestational age as a contextual modifier of pain, thus adjusting the pain score to account for the preterm's limited ability to mount a robust pain response due to immaturity.

Sedation scores range from 0 to −10. Whereas a study by Hillman and colleagues reported that the N-PASS sedation score was significantly correlated with nursing bedside assessment, a study by Giordano and researchers found that the N-PASS reliably detected oversedation but failed to differentiate between levels of adequate sedation and undersedation (Giordano et al., 2014; Hillman, Tabrizi, Gauda, Carson, & Aucott, 2015). Further research is needed to determine optimal levels of sedation to maximize the ventilator benefits of the right sedation, while reducing the negative impact of oversedation on clinical outcomes.

Factors That Influence Pain

Pain is unique among neurologic functions because of the degree of plasticity in pain neurophysiology. Although structural and functional maturity is reached at an early age, anatomic and functional changes occur throughout life and are related to the effects of each pain experience. This plasticity means that the perception and meaning of pain are unique to each individual and are not determined by maturation alone but are influenced by many individual and contextual factors. Currently available methods to assess pain in infants do not adequately or quantitatively incorporate all aspects of the context of pain that influence the pain experience. Thus, the clinician must remain cognizant of the ways in which perception of pain may be positively or negatively influenced by these factors and subjectively incorporate them into the assessment of pain. These factors do not influence pain in isolation but are listed separately for clarity.

Behavioral State. The behavioral state of the infant, ranging from deep sleep to awake and crying, acts as a moderator of behavioral pain responses. The behavioral state of the infant immediately before the painful stimulus affects the robustness of the response. Infants in awake states demonstrate more robust reactions to pain than infants in sleep states. Infants in a drowsy or deep-sleep state will show less vigorous facial expression in response to heelstick than do infants who are alert or aroused before the heelstick (Grunau & Craig, 1987; Mathai, Naresh, & Sahu, 2011; Stevens, Johnston, & Horton, 1994).

Gestational Age. Gestational age affects infant pain responses, with younger infants displaying fewer and less vigorous behavioral responses to pain (Gibbins & Stevens, 2003; Stevens et al., 1994, 1996, 1999). In addition, preterm neonates may demonstrate unique behaviors in response to noxious stimuli. Several researchers have used the Newborn Individualized Developmental Care and Assessment Program (NIDCAP, Children's Hospital, Boston, MA) to examine responses of preterm neonates to a heelstick procedure and found that preterm neonates may uniquely respond to acute pain by increased flexion and extension of arms and legs, finger splay, fisting, frowning, and hand-on-face behaviors (Holsti, Grunau, Oberlander, & Whitfield, 2004; Walden et al., 2001).

Previous Pain Experience. Previous pain experience of preterm neonates may lead to alterations in pain signal processing. Infants who were subjected to more frequent painful procedures in the NICU had decreased behavioral and increased cardiovascular responses compared with infants who experienced less pain, even after controlling for gestational age–related differences in pain expression (Johnston & Stevens, 1996; Stevens et al., 1999).

Caregiver Handling. Term and healthy preterm newborns who were handled or immobilized before a heelstick procedure exhibited greater physiologic and behavioral reactivity, thus indicating that previous stress may result in greater instability in response to pain (Porter, Wolf, & Miller, 1998).

MANAGEMENT OF NEONATAL PAIN

Leaving pain untreated or undertreated is considered unethical due to the availability of validated assessment tools, multimodal treatment options, and abundance of research on neonatal pain (Carter & Brunkhorst, 2017). The goals of pain management in infants are (1) to minimize the intensity, duration, and physiologic cost of the pain experience; (2) to maximize the infant's ability to cope with and recover from the painful experience; and (3) to maintain a balance between pain relief and adverse effects of analgesics (Carbajal, Gall, & Annequin, 2004). Depending on duration and severity, pain may be successfully managed with nonpharmacologic comfort measures and/or pharmacologic therapies.

Prevention of Pain

Painful procedures in the NICU are unavoidable; therefore, it is vital that caregivers assist infants to cope with and recover from necessary but painful clinical procedures. Research suggests that increased neonatal procedural pain is associated with reduced white matter and impaired early brain development in very preterm infants (Brummelte et al., 2012). Therefore, strategies to prevent pain should be employed whenever possible, including grouping blood draws to minimize the number of venipunctures per day, establishing central vessel access when appropriate to minimize vein and artery punctures, and limiting adhesive tape and gentle removal of tape to minimize epidermal stripping.

Nonpharmacologic Comfort Management

Nonpharmacologic pain management is useful for short-term, mild to moderate pain in neonates and in conjunction with pharmacologic modalities for more severe pain (Committee on Fetus and Newborn and Section on Anesthesiology and Pain Medicine, 2016). Nonpharmacologic strategies are hypothesized to directly reduce pain by (1) blocking nociceptive transduction or transmission; (2) activating descending inhibitory pathways; or (3) activating attention or arousal systems that modulate pain. Nonpharmacologic strategies such as hand or blanket swaddling, breastfeeding, nonnutritive sucking (NNS), oral sucrose, and skin-to-skin contact may help minimize neonatal pain and stress while maximizing the infant's own regulatory and coping abilities (Carter & Brunkhorst, 2017).

Environmental Modifications. Infants who are sick or in pain will need changes in the environment to decrease stress and provide a healing atmosphere. These modifications generally include dim lighting, decreased noise, and reduced activity around the bedside (Carter & Brunkhorst, 2017).

Swaddling or Facilitated Tucking. Containment strategies to limit excessive, immature motor responses have been demonstrated to be effective in minimizing pain responses in preterm neonates. Swaddling is thought to reduce pain by providing gentle stimulation across the proprioceptive, thermal, and tactile sensory systems. Several studies have been conducted in the preterm population using either hand or blanket swaddling. A hand-swaddling technique known as "facilitated tucking" (holding the infant's extremities flexed and contained close to the trunk with hand flat on back or containing bottom and cupping the head) has been shown to

attenuate pain responses in preterm neonates by decreasing heart rates, increasing oxygen saturations, decreasing crying time and sleep disruption times, and reducing pain scores during heelstick procedures and endotracheal suctioning (Cignacco et al., 2012; Hartley, Miller, & Gephart, 2015; Obeidat, Kahalaf, Callister, & Froelicher, 2009; Wallace & Jones, 2017).

NNS. NNS is the provision of a pacifier into the mouth to promote sucking without the provision of breast milk or formula for nutrition. NNS is thought to produce analgesia through stimulation of orotactile and mechanoreceptors when a pacifier is introduced into the infant's mouth. NNS is hypothesized to modulate transmission or processing of nociception through mediation by the endogenous nonopioid system (Blass, Fitzgerald, & Kehoe, 1987; Field, 2017; Wallace & Jones, 2017).

NNS has been shown to reduce pain responses in both term and preterm neonates (Pillai Riddell et al., 2011) during immunizations (Liaw et al., 2011) and heelstick procedures (Liaw et al., 2010). A study by Stevens and colleagues found that pain relief was greater in infants who received both NNS and sucrose (Carter & Brunkhorst, 2017; Stevens et al., 1999). A study by Campos (1989) reported a rebound in distress occurred when the NNS pacifier was removed from the infants' mouths. Therefore, the efficacy of NNS is immediate but appears to terminate almost immediately on cessation of sucking (Campos, 1989).

Sucrose. Sucrose with and without NNS has been the most widely studied nonpharmacologic intervention for infant pain management. Sucrose is a disaccharide composed of fructose and glucose. A systematic review of 74 randomized controlled trials of full-term and preterm infants (N = 7,049) found that sucrose is safe and effective for reducing procedural pain in term and preterm neonates, particularly heelstick and venipuncture procedures and intramuscular injections (Stevens, Yamada, Ohlsson, Haliburton, & Shorkey, 2016). Although some additional benefit has been reported with doses up to 50%, doses of 24% sucrose or greater are most effective. A pain-reduction response is noted with dose volumes ranging from 0.05 to 2 mL of a 24% solution administered approximately 2 minutes before the painful stimulus (Stevens et al., 2016). This 2-minute time interval appears to coincide with endogenous opioid release triggered by the sweet taste of sucrose (Blass, 1994). The effect of sucrose appears to last approximately 4 minutes; therefore, repeated doses may be necessary if procedures are prolonged (Stevens et al., 2016). The use of sucrose in combination with other behavioral interventions such as NNS, skin-to-skin holding, and containment may enhance the analgesic effect of sucrose.

Although relatively few contraindications to the provision of swaddling and NNS for management of pain in neonates exist, the absolute safety of sucrose has not been determined. Rare instances of choking and decreased oxygen saturation, all resolving spontaneously, have been reported (Gibbins et al., 2002). Although a study by Willis and colleagues reported an association between sucrose and necrotizing enterocolitis (NEC), other research findings found no significant differences in incidence rates for NEC between infants who received repeated doses of sucrose over 28 days of life compared with control groups (Stevens et al., 2005; Willis, Chabot, Radde, & Chance, 1977). Sucrose should be used with caution in extremely preterm neonates, critically ill newborns, neonates with unstable blood glucose levels, and infants at risk for NEC. Furthermore, sufficient evidence of the safety of repeated doses of sucrose in neonates to recommend its widespread use for repeated painful procedures is lacking (Stevens et al., 2016). Johnston and colleagues reported that preterm infants less than 31 weeks' postmenstrual age who received repeated doses of sucrose for painful procedures showed poorer neurodevelopmental scores at 36 and 40 weeks (Johnston et al., 2002). However, a later study failed to demonstrate significant differences on neurobiologic risk status outcomes between preterm infants who received sucrose plus pacifier, water plus pacifier, or the standard care group (Stevens et al., 2005).

Seventy-one neonates between 24 and 32 weeks' gestational age were studied to determine the effects of sucrose and facilitated tucking alone and in combination. Sucrose is more effective than facilitated tucking alone though there is additional benefit during the recovery phase when sucrose and facilitated tucking are combined (Cignacco et al., 2012).

Skin-to-Skin Contact (Kangaroo Mother Care). Skin-to-skin contact, or kangaroo mother care, has been demonstrated to significantly reduce pain responses in term newborns and preterm neonates greater than 28 weeks' gestational age during heelstick and single painful procedures (Johnston et al., 2003, 2008, 2017). The study by Johnston et al. (2008) also showed that preterm neonates between 28 and 32 weeks' gestational age demonstrated a shorter time to recovery as compared with control neonates who were swaddled and lying prone in an incubator during the heelstick procedure.

Pharmacologic Management

Pharmacologic agents are often required to alleviate moderate to severe procedural, postoperative, or disease-related pain in neonates. Systemic analgesia, topical anesthetics, nonopioid analgesia, and adjunctive medications are reviewed. The most commonly used drugs for analgesia in neonates are listed in Table 23.2.

Opioids. Opioid analgesics are considered the gold standard for pain relief. Opioids are often the preferred choice to manage moderate to severe pain in neonates. Morphine and fentanyl are the most commonly used opioids in the NICU, although other drugs may also be used for pain control in the neonatal population. Opioids have (1) potent analgesic effects, (2) ability to produce sedation but no amnesic or hypnotic effects, (3) few hemodynamic side effects, and (4) availability of antagonist drugs such as naloxone to reverse adverse side effects (Walter-Nicolet, Annequin, Biran, Mitanchez, & Tourniaire, 2010). The most common adverse effects include respiratory depression, bronchospasm, reduced gastrointestinal motility, urinary retention, and pruritus.

Morphine. Morphine is the gold standard for opioid analgesia in critically ill and postoperative neonates. Morphine has a slower onset of analgesia due to lower lipid solubility, especially in preterm neonates. The onset of action is 5 minutes, and the peak effect occurs at 15 minutes (Walter-Nicolet et al., 2010).

Morphine has few effects on the neonatal cardiovascular system in the well-hydrated neonate. Hypotension, bradycardia, and flushing are part of the histamine response to morphine and can be decreased by slow intravenous bolus administration (over 10–20 minutes) and optimizing intravascular fluid volume (Anand, 2007). Although relatively uncommon, the effects of histamine release may also cause bronchospasm in infants with chronic lung disease (Anand, 2007). Decreased intestinal motility and abdominal distention may also occur, causing a delay in the establishment of enteral feeding in the preterm neonate (Anand, 2007). Tolerance of enteral feeds may be improved by priming the gut with small volumes of milk.

Compared with fentanyl, morphine is less likely to cause dependence or withdrawal. Close monitoring and individual titration of the amount and frequency of doses for all neonates receiving morphine therapy is essential (Anand, 2007).

TABLE 23.2

COMMONLY USED DRUGS FOR ANALGESIA IN NEONATES

Drugs	Routes	Dose	Administration Notes
Opioid Analgesics			
Morphine	Intermittent IV, intramuscular, subcutaneous Continuous infusion Oral/parenteral ratio	0.05–0.2 mg/kg 0.01–0.02 mg/kg/hour	Give over at least 5 minutes Repeat as required (usually every 4 hours) Give loading dose of 0.1–0.15 mg/kg over 1 hour Oral dose is 3 to 5 times IV dose; for treatment of opioid dependence, begin at most recent IV morphine dose equivalent and taper 10%–20% per day as tolerated
Fentanyl	Intermittent IV Continuous infusion	0.5–4 mcg/kg 1–5 mcg/kg/hour	Repeat as required (usually every 2–4 hours) Tolerance may develop rapidly after constant infusion Adjust weaning schedule on the basis of withdrawal symptoms
Nonsteroidal Anti-inflammatory			
Acetaminophen	PO	12–15 mg/kg	Give loading dose of 20–25 mg/kg Give loading dose of 30 mg/kg Maintenance intervals: Term infants: give every 6 hours Preterm infants older than or equal to 32 weeks' PCA: give every 8 hours Preterm infants younger than 32 weeks' PCA: give every 12 hours
Local/Regional Anesthetics/Analgesia			
Eutectic mixture of local anesthetics	Topical	1–2 g	Apply and wrap with occlusive dressing; allow to remain intact for 60–90 minutes; remove and clean before procedure to avoid systemic absorption; monitor for methemoglobinemia
Local/Regional Anesthetics/Analgesia			
Liposomal lidocaine cream (4%)	Topical	1 g	Use only on normal, intact skin; prepare the area by washing with mild soap and water; DO NOT use alcohol; apply a small amount of cream and gently massage into the skin, then apply the remainder of the dose in a 1/4-inch thick layer and cover with an occlusive dressing at least 30 minutes before the procedure; remove cream and cleanse area before beginning procedure
Lidocaine 1%[a]	Subcutaneous	0.2–0.5 mL	Epinephrine should never be added to the lidocaine because of its vasoconstrictive properties and the risk of ischemia and necrosis; infiltrate area using 25 G needle approximately 3–8 minutes before procedure

[a]Data from Pinheiro, J. M., Furdon, S., & Ochoa L. F. (1993) Role of local anesthesia during lumbar puncture in neonates. *Pediatrics, 91*(2), 379–382. Retrieved from https://pediatrics.aappublications.org/ content/91/2/379; Regen, R., & Whitehill, J. (2012). Drug considerations in circumcision. *U.S. Pharmacist, 27*(3), HS-2-5. Retrieved from https://www.uspharmacist.com/article/drug-therapy-considerations-in-circumcision

IV, intravenous; PCA, postconceptual age.

Source: Data adapted from Young, T. E., & Mangum, B. (2010). *NeoFax* (23rd ed.). Montvale, NJ: Thomson Reuters and Lexicomp online.

The effect of morphine therapy on neurologic outcomes of preterm neonates is unclear (Zwicker et al., 2016). Although two large randomized controlled trials (NEOPAIN [Neurologic Outcomes and Pre-emptive Analgesia in Neonates] and the EPIPAGE [Etude Epidemiologique sur lest Petits Ages Gestationalles]) suggest that morphine therapy does not have an adverse effect on neurologic outcomes (Anand et al., 2004; Roze et al., 2008), a subsequent study evaluating neurobehavioral outcomes at 36 weeks of neonates enrolled in the NEOPAIN trial suggested that morphine analgesia may result in subtle neurobehavioral differences in preterm neonates (Rao et al., 2007).

The effectiveness of morphine for acute pain caused by invasive procedures remains unclear. Several studies support the effectiveness of morphine analgesia for acute pain (Anand et al., 1999; Taddio et al., 2006), whereas other studies have found no significant analgesic efficacy (Carbajal et al., 2005; Franck, Greenberg, & Stevens, 2000; Saarenmaa, Huttunen, Leppaluoto, Meretoja, & Fellman, 1999; Simons, van Dijk, van Lingen, et al., 2003).

Fentanyl. Randomized clinical trials in neonates have found that fentanyl is approximately 13 to 20 times more potent than morphine (Saarenmaa et al., 1999). Fentanyl is probably the most widely used analgesic in neonates and offers two distinct advantages over morphine (Anand, 2007). First, fentanyl causes less histamine release than morphine and may be more appropriate for neonates with hypovolemia or hemodynamic instability, congenital heart disease, or chronic lung disease (Walter-Nicolet et al., 2010). Second, fentanyl blunts increases in pulmonary vascular resistance. This finding makes it potentially useful in managing pain in neonates with persistent pulmonary hypertension (Walter-Nicolet et al., 2010).

Fentanyl has a more rapid onset (3 minutes) and shorter duration of action (30 minutes) compared with morphine and must be administered as a continuous infusion or as an intravenous bolus every 1 to 2 hours. Accumulation of fentanyl in fatty tissues with extended use may prolong its sedative and respiratory depressant effects and may be responsible for the rebound increase in plasma levels observed following discontinuation of therapy in neonates (Anand, 2007).

Tolerance may develop rapidly with fentanyl, especially with continuous infusions compared with bolus dosing. In addition, dependence and withdrawal are more significant with fentanyl as compared with morphine (Franck, Vilardi, Durand, & Powers, 1998).

Rarely, fentanyl can significantly reduce chest wall compliance (stiff chest syndrome). This naloxone-reversible side effect can be prevented by slow infusion (as opposed to rapid bolus administration) or concomitant use of muscle relaxants.

Prevention of Opioid Withdrawal Symptoms. The rise in opioid use in the United States has resulted in a fivefold increase in neonatal abstinence syndrome (NAS) in NICUs around the country. The incidence of NAS has dramatically risen from 1.19 per 1,000 hospital births in 2000, to 5.63 per 1,000 in 2012 (Sanlorenzo, Stark, & Patrick, 2018). Treatment of these infants may be based on whether there was polydrug use, duration of exposure, use near the time of delivery, and severity of symptoms.

Neonates who require opioid therapy for an extended period of time may develop physical dependence and withdrawal. Rapid weaning of opioids may lead to withdrawal symptoms such as irritability, crying, increased respiratory rate, jitteriness, hypertonicity, vomiting, diarrhea, sweating, skin abrasions, seizures, yawning, stuffy nose, sneezing, and hiccups. The goals of clinical management of opioid withdrawal are (1) to reduce withdrawal symptoms to promote regular sleep cycles and (2) to reduce agitation caused by care interventions (Anand et al., 2010). The prevalence of opioid withdrawal is greater in infants after continuous infusions of fentanyl than continuous infusions of morphine (Franck et al., 1998). Dominguez and colleagues reported a 53% incidence in opioid withdrawal in neonates who received a minimum of 24 hours of fentanyl by continuous infusion. In this study, the most significant risk factors for opioid withdrawal were higher total dose and longer infusion duration. In all neonates with withdrawal, onset of withdrawal symptoms occurred within 24 hours of discontinuation of the fentanyl infusion (Dominguez, Lomako, Katz, & Kelly, 2003).

Data are insufficient to determine the optimal weaning rate of opioids to prevent withdrawal symptoms in neonates on opioid therapy (Hudak, Tan, Committee on Drugs and the Committee on Fetus and Newborn, & American Academy of Pediatrics, 2012). Ducharme, Carnevale, Clermont, and Shea (2005) reported that adverse withdrawal symptoms in children who received continuous infusions of opioids and/or benzodiazepines could be prevented when the daily rate of weaning did not exceed 20% for children who received opioids/benzodiazepines for 1 to 3 days; 13% to 20% for 4 to 7 days; 8% to 13% for 8 to 14 days; 8% for 15 to 21 days; and 2% to 4% for more than 21 days, respectively.

Buprenorphine is gaining recognition for decreasing treatment days and length of hospital stay (LOS) in opioid-exposed infants with NAS (Kocherlakota, 2014; Sanlorenzo et al., 2018). Buprenorphine is a partial mu opioid agonist and administration is sublingual. Studies comparing buprenorphine with morphine or methadone showed from 29% to 46% reduction in length of treatment (Hall, Rice, Folger, & Wexelblatt, 2018; Kraft et al., 2017).

Abstinence scoring methods commonly used in the care of the infant with prenatal drug exposure must be employed in assessing the infant during withdrawal from prolonged opioid use. The Modified Finnegan's Neonatal Abstinence Scoring Tool (Hudak et al., 2012) is the most commonly used tool for assessment of NAS in the United States. Challenges associated with scoring include conducting the assessment when an infant is hungry or sleeping or taking an infant away from parents to assess (Sanlorenzo et al., 2018). Scores may be higher when an infant is irritable with hunger, separated from parents, or awakened leading to unnecessary treatment.

A novel approach to scoring (ESC) was used in a quality improvement project to improve care of NAS patients. The components of the tool are very simple and easy to use clinically and include:

- E = Eat: able to eat 1 or more ounces each feeding
- S = Sleeping: able to sleep for 1 hour or longer when uninterrupted
- C = Console: can be consoled within 10 minutes or less when upset

Outcome measures were average LOS, morphine usage, and associated costs of treatment/LOS. A total of 287 infants were enrolled: 55 in the baseline period, 188 during the intervention period, and 44 in the postimplementation period. Length of stay decreased on average from 22.4 to 5.9 days. Morphine usage decreased from 98% to 14% and costs were reduced from $44,824 to $10,289. There were no reported adverse events and no infants had to be readmitted for NAS (Grossman et al., 2017).

Specific guidelines and/or intervention algorithms guide physicians and staff during opioid weaning and have been utilized successfully by many hospitals (Kocherlakota, 2014). A strict guideline is reported to significantly decrease opioid treatment days, decrease hospital stay, and result in less need for adjunctive drug therapy (Sanlorenzo et al., 2018). If it is possible to treat an infant with NAS outside the NICU, then keeping the mother–infant dyad together is a priority.

Methadone. Methadone is a synthetic opioid that produces prolonged analgesia and has good oral bioavailability, thus making it an attractive option to manage NAS (Hudak et al., 2012). When an infant is being weaned from opioid therapy to a longer-acting oral medication such as methadone, the starting dose of methadone should be calculated to provide a dose equivalent to the dose of opioid the neonate is receiving (Hudak et al., 2012). Further weaning should then be accomplished on the basis of frequent reassessment to ensure that the patient is free of pain and withdrawal symptoms. Studies are needed to further establish the pharmacokinetics and dosing requirements of methadone in neonates.

Topical Application of Local Anesthetics. Topical anesthetics are useful for the management of procedure-related pain in neonates. While EMLA cream ([eutectic mixture of local anesthetics],

lidocaine, and prilocaine; Astra Pharmaceuticals, London) has the best evidence for use in neonates, tetracaine 4% gel (Ametop; Smith & Nephew, London) and liposomal lidocaine cream (LMX 4%; Ferndale Laboratories, Michigan) have also been used in neonates.

EMLA Cream. EMLA cream is approved for use in infants at birth with a gestational age of 37 weeks or greater for a variety of clinical procedures. EMLA produces topical anesthesia when applied as a cream to the surface of intact skin and then covered with an occlusive dressing. The primary concern with the use of EMLA is methemoglobinemia caused by prilocaine toxicity. Neonates, particularly preterm neonates, are at increased risk because of a thinner stratum corneum and less active NADH-dependent (*NADH* dehydrogenase) methemoglobin reductase enzymes that result in higher plasma levels (Sethna & Koh, 2000). Neonates who have anemia, sepsis, hypoxemia, or metabolic acidosis and who are receiving other methemoglobin-inducing drugs such as acetaminophen, phenytoin, phenobarbital, or nitroprusside may also be at increased risk for development of systemic toxicity (Sethna & Koh, 2000). Although it is not routinely recommended for use in preterm neonates, one study found that a single dose of 0.5-g EMLA cream applied for 60 minutes to the intact skin of preterm infants older than 30 weeks' gestation did not result in significant increases in blood methemoglobin concentrations (Taddio, Shennan, Stevens, Leeder, & Koren, 1995). In addition to the risk of methemoglobinemia, local skin reactions have been noted with EMLA cream and have included blanching, redness, and transient purpuric lesions (Sethna & Koh, 2000). Policies and procedures regarding application of EMLA cream should be established to maximize pain relief while minimizing the potential side effects.

Three primary factors determine the effectiveness of EMLA cream: dose, size of application area, and duration of exposure (Sethna & Koh, 2000). The depth of penetration of EMLA is approximately 2 to 3 mm (Walter-Nicolet et al., 2010). The recommended dose in neonates older than 37 weeks is 1 to 2 g applied to the procedure site 60 to 90 minutes before the procedure and covered with an occlusive dressing (Anand, 2018). Multiple studies document the efficacy of EMLA in reducing pain associated with venipunctures and circumcisions (Anand et al., 2005). EMLA has also been documented to be effective in managing pain associated with lumbar puncture (Kaur, Gupta, & Kumar, 2003). EMLA has not been shown, however, to be effective in managing pain associated with heelstick procedures (Anand et al., 2005).

Tetracaine 4% Gel. Tetracaine 4% gel (Ametop; Smith & Nephew, London) has also been investigated in neonates for management of procedural pain. Tetracaine 4% gel produces anesthesia within 30 to 45 minutes of application and has duration of action between 4 and 6 hours (O'Brien et al, 2005). A meta-analysis of six randomized controlled trials comparing tetracaine with EMLA found tetracaine significantly reduced pain associated with intravenous cannulation compared with EMLA. However, tetracaine is ineffective in reducing the pain of heelprick and peripherally inserted central catheters in neonates (Lander, Weltman, & So, 2006). The most commonly reported local skin reaction is transient local erythema. Tetracaine gel is not recommended for use in preterm infants or full-term infants under 1 month of age (Hsu, 2018).

LMX 4%. Another topical local anesthetic currently used in pediatrics for management of procedural pain is liposomal lidocaine cream (LMX 4%; Ferndale Laboratories, Michigan). Several studies have evaluated the efficacy of LMX and EMLA and found a 30-minute application of LMX to be as effective as a 60-minute application of EMLA for producing topical anesthesia for peripheral intravenous access in older children (Eichenfield, Funk, Fallon-Friedlander, & Cunningham, 2002; Kleiber, Sorenson, Whiteside, Gronstal, & Tannous, 2002; Koh et al., 2004). Another study found LMX to be equally effective as EMLA in reducing the pain of circumcision in term newborns (Lehr et al., 2005). LMX may offer an improved risk–benefit profile compared with EMLA, considering the faster onset of action and no risk of methemoglobinemia. LMX does, however, contain an excipient of benzyl alcohol that is known to cause serious respiratory compromise, gasping respirations, metabolic acidosis, and death. Other medications used in the NICU contain benzyl alcohol, propylene glycol, and ethanol, and so providers must be careful when ordering these products to avoid the accumulation of benzyl alcohol and other preservatives capable of toxicity. Excipients are chemical additives to prolong shelf life of medications, increase absorption, manage release of active ingredients, and even enhance taste. Recent studies have shown that neonates in the NICU may be exposed to high levels of excipients, sometimes higher than recommended adult doses (Akinmboni, Davis, Falck, Bearer, & Mooney, 2018; Valeur, Hertel, Lundstrøm, & Holst, 2018). Further studies in neonates are needed to establish the safety and efficacy of LMX for management of procedural pain in neonates.

Nonopioid Analgesics

Acetaminophen. Acetaminophen, also known as paracetamol, is a nonopioid analgesic for short-term management of mild to moderate pain in neonates, but is ineffective for acute procedure-related pain. Acetaminophen has been commonly administered in neonates as an oral or rectal preparation. A study by Zuppa et al. (2011) reports the safety of intravenous administration of acetaminophen in neonates. When intravenous acetaminophen is administered concurrently with opioid analgesia, the effect is additive and allows a reduction in dosages of both drugs, resulting in fewer adverse side effects (Menon, Anand, & McIntosh, 1998; Ohlsson & Shah, 2016).

Little information is available on the pharmacokinetics of acetaminophen administration in neonates, especially administration by the rectal route. Peak concentrations of analgesic effect are reached approximately 60 minutes after an oral dose (Lexicomp, 2018). Elimination half-life is approximately 3 hours in term neonates, but can be as long as 11 hours in more preterm neonates requiring longer dosing intervals with decreasing gestational ages (Young & Mangum, 2011). Acetaminophen is metabolized almost entirely by hepatic conjugation, and elimination may be prolonged in neonates with liver dysfunction. Acetaminophen dosing according to tables with gestational age–related volumes is the safest way when working with preterm and term neonates (Lexicomp, 2018).

At therapeutic doses, acetaminophen is well tolerated and has a low toxicity. Because acetaminophen does not inhibit prostaglandin synthesis in tissues other than the brain, common side effects of nonsteroidal anti-inflammatory drugs—such as inhibition of platelet function, renal insufficiency, and gastrointestinal irritation—do not occur (Anand, Menon, Narsinghani, & NcIntosh, 2000). The primary concern of acetaminophen is liver damage, but this should not be a concern in neonates if standard doses are used (Lexicomp, 2018).

The use of acetaminophen in the first year of life has been reported to increase the risk of asthma, rhinoconjunctivitis, and eczema at 6 to 7 years of age (Beasley et al., 2008). A large Norwegian study provides additional evidence that prenatal and infant acetaminophen is independently associated with increased risk of asthma at 3 and 7 years (Magnus et al., 2016). In a multicenter, prospective, randomized, double-blind, parallel-group study of 300 children ages 12 to 59 months with mild, persistent asthma,

acetaminophen was no more likely to be associated with asthma exacerbation and the need for glucocorticoids than ibuprofen (Sheehan et al., 2016).

Further studies are needed to confirm these long-term adverse effects. Routine prophylactic use of acetaminophen at the time of vaccination is not recommended due to a potential reduction in antibody response (Prymula et al., 2009). In infants, paracetamol before vaccination may interfere with adequate immune responses to pneumococcal antigens, whereas ibuprofen weakens responses to pertussis and tetanus antigens. Antipyretics for fever prophylaxis before and during infant vaccination may need to be reconsidered (Wysocki et al., 2017).

Use of Adjunctive Drugs. In the NICU, the use of sedatives, alone or in combination with analgesics, is controversial. **Quality and Safety: Sedatives suppress the behavioral expression of pain, have no analgesic effects, and can even increase pain. Sedatives should only be used when pain has been ruled out.** When administered with opioids, sedatives may allow more optimal weaning of opioids in critically ill, ventilator-dependent neonates who have developed tolerance from prolonged opioid therapy. No research has been done to determine the safety or efficacy of combining sedatives and analgesics for the treatment of pain in infants. The most commonly administered sedatives in the NICU are benzodiazepines and chloral hydrate.

Benzodiazepines

Midazolam. Midazolam is a short-acting benzodiazepine that is frequently used as a hypnosedative in neonates. Safety concerns with the use of midazolam in neonates have been reported because of the large number of adverse neurologic effects associated with midazolam in term and preterm neonates. Severe hypotension, seizures, respiratory depression, and respiratory arrest have been reported in neonates following continuous infusions or rapid bolus administration (Lexicomp, 2018; Young & Mangum, 2011). Due to uncertainty about its safety, a Cochrane review concluded that data are insufficient to promote the use of intravenous midazolam infusions for sedation in neonates (Ng, Taddio, & Ohlsson, 2017).

Diazepam. Diazepam is not recommended for administration in neonates because of its very prolonged half-life (20–50 hours), its long-acting metabolites, and concern about the benzyl alcohol content. The dose of benzyl alcohol preservative in diazepam is, however, below the dose known to cause fatal toxicity in premature neonates (100–400 mg/kg/day). **Emergency Alert: Caution must be used to ensure other medications do not contain benzyl alcohol that could result in accumulation and higher doses that exceed the toxic amounts. Diazepam displaces bilirubin from albumin-binding sites, thereby increasing the neonate's risk of kernicterus** (Anand et al., 2000).

Chloral Hydrate. Chloral hydrate has been used in single doses to sedate neonates during pulmonary function, radiographic, and other diagnostic testing for which the patient must lie still. The onset of action is 10 to 15 minutes (Young & Mangum, 2011). Adverse effects include bradycardia, gastric irritation, and paradoxical excitement (Young & Mangum, 2011). Although clinically effective, concern has been raised about the potential carcinogenic effects of chloral hydrate administered to mice (Young & Mangum, 2011). The extremely long half-life of chloral hydrate increases the risk of toxicity with repeated administration. It is considered as inferior sedation to other options and comes with a high frequency of adverse reactions. Alternative sedatives (i.e., benzodiazepines) should be used when possible (Lexicomp, 2018).

MANAGEMENT OF SPECIFIC PAIN TYPES

Pain management techniques may vary on the basis of pain type and clinical situation. This section reviews special issues related to procedural pain, postoperative pain, preemptive analgesia for mechanical ventilation, and pain management at EOL.

Procedural Pain

It has been estimated that newborn infants, particularly those born preterm, are routinely subjected to an average of 61 invasive procedures performed from admission to discharge, with some of the youngest or sickest infants experiencing more than 450 painful procedures during their hospital stays (Barker & Rutter, 1995). Many of the procedures commonly performed in the neonate cause moderate to severe pain, with average pain scores of 5 on a 10-point scale (Simons, van Dijk, van Lingen, et al., 2003). Substantial numbers of failed attempts at procedures dramatically increase the number of painful procedures that neonates are subjected to. Simons and colleagues found that the percentages of failed procedures for insertion of central venous catheters, insertion of peripheral arterial catheters, and intravenous cannula insertion were 45.6%, 37.5%, and 30.9%, respectively (Simons, van Dijk, van Lingen, et al., 2003). **Quality and Safety: These frequent, invasive, and noxious procedures occur randomly in the NICU, and many times are not routinely managed with either pharmacologic or nonpharmacologic interventions (Carbajal et al., 2008; Johnston, Barrington, Taddio, Carbajal, & Filion, 2011).** Anand and the International Evidence-Based Group for Neonatal Pain (2001) provide guidelines for preventing and treating neonatal procedural pain. Strategies for the management of procedures commonly performed in the NICU are summarized in Table 23.3 (Anand & the International Evidence-Based Group for Neonatal Pain, 2001).

Local anesthesia may not be sufficient for procedures that affect deeper tissue, such as chest tube insertion or surgical cut down of vessels. Central analgesia is then required to prevent pain. For the nonventilated patient, in whom concern for the respiratory depressant effects of opioids exists, one-half the standard dose may be administered. The infant's respiratory status and responsiveness to pain stimuli can then be assessed before further drug administration. For the infant who is receiving opioid analgesics on a regular basis, a controlled infusion of a bolus dose may be required to provide adequate analgesia during an invasive procedure.

Postoperative Pain

Anticipating and planning is essential to managing postoperative pain. Adequate analgesia is important during the immediate postoperative period for the optimal recovery of the patient. Unrelieved pain can interfere with ventilation and delay weaning. In general, it is thought that the use of low-dose continuous infusions of opioid analgesics provides more constant, effective pain relief with less medication than repeated, intermittent scheduled doses of opioids (Spruill & LaBrecque, 2017). Analgesia is required as long as pain assessment scales along with nursing judgment indicate ongoing pain. Careful weaning may be needed following treatment, especially if the surgery was extensive.

Preemptive Analgesia for Mechanical Ventilation

Opioids are frequently used to sedate, promote respiratory synchrony, produce physiologic stability, and relieve pain or discomfort in ventilated neonates. However, a systematic review and meta-analysis of 13 studies on 1,505 infants concluded that there is insufficient evidence

TABLE 23.3

SUGGESTED MANAGEMENT OF PAINFUL PROCEDURES COMMONLY PERFORMED IN THE NICU

	Procedure	Gentle Technique	NNS ± Sucrose	Containment	Skin-to-Skin Holding	Topical Anesthetic	Opioids	Other/Notes
Mild	Tape removal	√	√	√				
	Endotracheal suctioning	√	√	√	√			
	Oro/nasogastric tube insertion	√	√	√	√			
	Umbilical catheterization	√	√	√				
	Intramuscular injection	√	√	√	√	√		
	Venipuncture/ arterial puncture	√	√	√	√	√		
	Heel lance	√	√	√	√			Use spring-loaded lancet Consider venipuncture for term and older preterm infants
Pain Intensity	Eye examination	√	√	√		√	√	Retinal surgery should be considered major surgery, and opioids should be provided
	Percutaneous/ arterial venous line placement	√	√	√		√	√	
	Endotracheal intubation	√		√			√	Use combination of atropine, morphine/ fentanyl, and nondepolarizing muscle relaxant
	Chest tube insertion	√		√		√	√	Consider subcutaneous infiltration of lidocaine
Severe	Circumcision	√	√	√		√		Dorsal penile nerve block or other regional block

Source: Data from Anand, K. J., & The International Evidence-Based Group for Neonatal Pain. (2001). Consensus statement for the prevention and management of pain in the newborn. *Archives of Pediatrics and Adolescent Medicine, 155*(2), 173–180. doi:10.1001/archpedi.155.2.173

available to recommend the routine use of opioids in mechanically ventilated neonates (Bellu, de Waal, & Zanini, 2010). These recommendations were attributed to failure to decrease pain scores during invasive procedures as well as the lack of overall benefits of morphine therapy on reduction of adverse outcomes such as death, intraventricular hemorrhage, and periventricular leukomalacia.

Pain Management at EOL

Compassionate care and relief of pain and suffering at EOL is a fundamental right of all individuals. Neonates who die as a result of a fatal neonatal illness deserve a good death. According to the Institute of Medicine, "a decent or good death is one that is: free from avoidable distress and suffering for patients, families, and caregivers; in general accord with patients' and families' wishes; and reasonably consistent with clinical, cultural, and ethical standards" (Committee on Palliative and End-of-Life Care for Children and Their Families, Board on Health Sciences Policy, & Institute of Medicine, 2003, p. 40). The quality of the dying process in the NICU is affected by a complex interaction of infant, parent, and caregiver factors (Fortney & Steward, 2014). In 2013, the American Academy of Pediatrics published a policy statement on pediatric palliative care and hospice care, yet significant variation remains in protocols addressing comfort care in pediatrics at EOL (American Academy of Pediatrics Section on Hospice and Palliative Medicine and Committee on Hospital Care, 2013; Haug et al., 2018). **Quality and Safety: Haug et al. (2018) reported that 45% of reporting institutions did not have neonatal comfort care guidelines and, of those reporting, 19% did not address pain symptom management.**

Pain assessment is extremely challenging in neonates at EOL. Caregivers must often consider risk factors for pain and rely on physiologic measures such as increases in heart rate and decreases in oxygen saturation to make pain management decisions. However, using a pain scale to measure pain in neonates at EOL remains a clinical standard as it provides an objective approach to assessing pain and facilitates improved communication about the infant's pain between professionals as well as with the infant's parents (Carter & Jones, 2013).

Pain management at EOL primarily centers on the provision of opioids to minimize pain and nonpharmacologic therapies to enhance the infant's comfort level (Walden, 2001). Continuous infusions of opioid therapy such as morphine and fentanyl are often required to manage pain at EOL and should be titrated to desired clinical response (analgesia). Opioid doses well beyond those described for standard analgesia are often required for infants who are in severe pain or who have developed tolerance (decreasing pain relief with the same dosage over time) after the prolonged use of opioids (Partridge & Wall, 1997). Physiologic comfort measures may palliate pain and distressing symptoms in infants at EOL and include reduction of noxious stimuli, organization of caregiving, and positioning and containment strategies (Walden, Sudia-Robinson, & Carrier, 2001).

A request for a palliative care consult often makes parents struggle with the decision as they often perceive this as "giving up" on their infant. Conversely, palliative care services may provide an added layer of support to parents and the healthcare team caring for an infant at EOL (Currie et al., 2016).

PARENTS

Nurses who care for the infant in pain must care for the infant's family as well. Parents have many concerns about their infants' pain and about the interventions used in the treatment of pain (Franck, Allen, Cox, & Winter, 2005; Gale, Franck, Kools, & Lynch, 2004). Several research studies have reported common barriers and facilitators of parental involvement in neonatal pain management (Franck, Oulton, & Bruce, 2012; Marfurt-Russenberger, Axelin, Kesselring, Franck, & Cignacco, 2016; Palomaa, Korhonen, & Polkki, 2016). Barriers often cited include parental emotional state, not wanting to be in the way, lack of knowledge, competing home and life requirements, medical equipment or health status of the infant, and unsupportive staff attitudes and paternalism toward parents. Parental suggestions for improving infant pain management have included increased education and advanced preparation on how to comfort their infant during painful procedures, increased use of standardized protocols for managing pain consistently, and family-friendly space and environment that supports parental presence and participation in their infant's pain relief (Franck et al., 2012; Marfurt-Russenberger et al., 2016; Palomaa et al., 2016).

A source of parental stress often occurs when there is a mismatch between parent and staff perceptions of the infant's pain (Gale et al., 2004). It is important to provide parents with consistent information about pain assessment and management. Debriefing with parents following a pain experience is a strategy that can be used to minimize disagreements between parents and nurses regarding pain intensity in the infant and may increase the potential for meaningful collaboration in improving the infant's pain care in the NICU.

Parents should be encouraged to participate in providing nonpharmacologic comfort measures to their infants during minor painful procedures. Several studies have shown that facilitated tucking by parents is an effective and safe pain management method during painful procedures in the NICU (Axelin, Lehtonen, Pelander, & Salantera, 2010; Axelin, Salantera, Kirjavainen, & Lehtonen, 2009; Axelin, Salantera, & Lehtonen, 2006). Depending on the nature of the medical procedure, increasing parental participation in providing comfort measures to their infant during painful procedures may help to moderate parental stress and optimize the parent–infant relationship (Miles & Holditch-Davis, 1997).

NEONATAL NURSE'S ROLE AND RESPONSIBILITIES

Provision of comfort and relief of pain are two primary goals of nursing care. To accomplish these goals, neonatal nurses must (1) prevent pain when possible, (2) assess pain in their neonatal patients who cannot verbalize their subjective experience of pain, (3) provide relief or reduction of pain through implementation of nonpharmacologic and/or pharmacologic measures, and (4) assist the infant in coping when pain cannot be prevented.

The effective management of infant pain requires nurses to collaborate with each other, with physicians, and with the infant's parents. Nurses must effectively communicate assessments and recommendations in an objective, concise manner and advocate for pain relief strategies with responsible healthcare team members. Neonatal nurses must remain informed about professional standards and clinical guidelines related to pain assessment and management in neonates. The nurse should also participate in ongoing pain education and review of new research and scientific developments.

SUMMARY

Pain in neonates is often assessed and managed inadequately in a large proportion of neonates in the NICU. It is clear, however, that caring for infants in pain requires attention not only to the immediate effects but also to the long-term developmental consequences of pain and pain treatment. Through ongoing research, objective assessment, effective collaboration, and systematic application of treatment plans, nurses will achieve greater comfort for individual patients and add to the body of knowledge in this rapidly evolving field.

CASE STUDY

■ **Identification of the Problem.** Term female infant with pain related to probable epidermolysis bullosa (EB) and extensive blistering of lower extremities

■ **Assessment: History and Physical Examination.** The term, 3,600-g female was born via vaginal delivery to a 19-year-old, unmarried, Hispanic, G2 P2, mother with minimal prenatal care. Maternal labs were unremarkable, including negative history for herpes. Maternal history positive for previous infant with confirmed EB. At birth, the infant was noted to have a vigorous respiratory effort at birth with Apgars 9 and 9 at 1 and 5 minutes of life, respectively. Significant bullous skin lesions were noted on the right lower leg and left ankle. She was transferred to the NICU for care.

Once in the NICU, she was placed in a dual radiant warmer/incubator bed and placed on continuous cardiorespiratory monitoring. An umbilical venous line was placed. Blood was sent for complete blood count (CBC) with differential and blood culture. Intravenous fluids were started along with small feedings of expressed breast milk or formula.

Physical examination on admission to the NICU was:

- Vital signs: heart rate 172; respiratory rate 38; temperature 97.6 axillary; blood pressure 68/47 MAP 54
- General: term-appearing infant with signs of pain and distress with handling
- HEENT: anterior fontanelle soft, flat, and large; sutures approximated; normocephalic; red reflex deferred; nares patent; mucous membranes moist and pink
- RESP: bilateral lung sounds clear and equal; respirations unlabored and of normal rate; no retractions, grunting, or nasal flaring
- CV: regular rate and rhythm. S_1 and S_2 present without murmur; strong and equal brachial and femoral pulses; capillary fill time less than 3 seconds
- ABD: soft and slightly rounded; normal bowel sounds; no hepatosplenomegaly
- Genitourinary: female genitalia appropriate for gestation; anus patent and appropriately positioned
- NEURO: Normal tone and activity; good grasp, suck, Moro; irritable with crying and facial grimacing
- SKIN: pink and warm; significant skin lesions on the right lower leg and left ankle
- Extremities: normotonic; full range of motion of all extremities; spine straight, midline without deformity

■ **Diagnoses**

- Term infant with probable EB
- Pain related to skin lesions

■ **Diagnostic Tests**

- CBC: WBC 13.2; Hgb 17; Hct 47.5; Plt 60; Segs 67; Lymphs 15; Monos 4; Eos 0; Bands 12
- Glucose 93
- Chromosome panel: pending
- Will need skin biopsy and other tests as determined by consultations with Genetics and Dermatology for final diagnosis

■ **Development of Management Plan for Pain**

1. Use CRIES to assess for pain with vital signs and before, during, and after procedures or dressing changes.
2. Strategies for prevention of pain: Vital signs per monitor. Reduced frequency of BPs to every day to reduce friction to the skin. If nasogastric tube is needed for feedings, secure with nonadhesive methods such as TubiFast or silicone tape for fragile skin.
3. Dysphagia may occur secondary to pain, oral blistering, and scarring. Use a Haberman or Lamb's nipple to reduce oral friction with nippling. Consult with pharmacy regarding oral topical anesthetic to be administered before nippling.
4. Protect skin by using dressings on bony prominences, egg-crate mattresses, sheepskins, and moist healing environment; avoiding tape; and avoiding trauma. Use petrolatum-based emollients covered with antibiotic ointments and nonstick dressings (e.g., Mepitel® dressings). Wrapping gauze, cotton mesh, or self-adhering elastic wrap (e.g., Coban™) around the dressing can protect and reduce friction.
5. Remove dressings carefully using gentle technique. Consider removing during bathing.
6. Reduce frequency of NICU interventions such as temperature taking, blood pressures, weighing, and so on.
7. Use mittens for the baby's hands and feet.
8. Administer fentanyl pro re nata (PRN) for CRIES scores of 5 or above. Consider weaning to an oral opioid when intravenous access is no longer needed.
9. Administer fentanyl before dressing changes and procedures anticipated to be of moderate to severe pain intensity.
10. Consult Dermatology and Wound Care for further recommendations to maintain skin integrity and manage open wounds.
11. Educate parents on how to provide protective, prophylactic, and therapeutic care for their infant with EB.

EVIDENCE-BASED PRACTICE BOX

Reducing Pain Associated With Screening for Retinopathy of Prematurity

Infants born less than 1,500 g or less than 32 weeks are routinely subjected to necessary ophthalmologic screening for retinopathy of prematurity (ROP). Screening examinations are a significant source of pain and discomfort and are associated with physiologic instability in preterm neonates. Dempsey and McCreery (2011) published a Cochrane systematic review to determine the effect of instillation of topical anesthetic eye drops on pain responses of preterm neonates undergoing ROP screening. Only two randomized crossover studies were identified for inclusion in the analyses. The authors concluded that the administration of proparacaine eye drops at least 30 seconds before the examination was associated with a reduction in pain scores, but was not effective in eliminating pain. The authors recommended that future studies should address the role of both nonpharmacologic and pharmacologic interventions, including different

(*continued*)

EVIDENCE-BASED PRACTICE BOX (*continued*)

local anesthetic agents, NNS, sucrose, and swaddling to reduce pain associated with this common procedure.

Investigators in a double-blind randomized controlled trial of 60 preterm infants gave topical anesthetic drops, then compared breast milk, sucrose, and distilled water before and after ROP exam. Due to the shorter recovery time with breast milk, they recommend breast milk over sucrose for pain management of ROP eye exams. The breast milk group also had lower mean heart rates and higher oxygen saturations than the sucrose group (Taplak & Erdem, 2017).

References

Dempsey, E., & McCreery, K. (2011). Local anesthetic eye drops for prevention of pain in preterm infants undergoing screening for retinopathy of prematurity [Meta-analysis review]. *Cochrane Database of Systematic Reviews,* (9), CD007645. doi:10.1002/14651858.CD007645.pub2

Taplak, A. Ş., & Erdem, E. (2017). A comparison of breast milk and sucrose in reducing neonatal pain during eye exam for retinopathy of prematurity. *Breastfeeding Medicine, 12*(5), 305–310. doi:10.1089/bfm.2016.0122

REFERENCES

Agency for Health Care Policy and Research. (1992). *Acute pain management in infants, children, and adolescents: Operative and medical procedures: Quick reference guide for clinicians.* Rockville, MD: Department of Health and Human Services.

Ahn, Y. (2006). The relationship between behavioral states and pain responses to various NICU procedures in premature infants (Research Support, Non-U. S. Gov't). *Journal of Tropical Pediatrics, 52*(3), 201–205. doi:10.1093/tropej/fmi099

Akinmboni, T. O., Davis, N. L., Falck, A. J., Bearer, C. F., & Mooney, S. M. (2018). Excipient exposure in very low birth weight preterm neonates. *Journal of Perinatology, 38*(2), 169–174. doi:10.1038/jp.2017.165

American Academy of Pediatrics Committee on Fetus and Newborn and Section on Anesthesiology and Pain Medicine. (2016). Prevention and management of procedural pain in the neonate: An update. *Pediatrics, 137*(2), 1–13. doi:10.1542/peds.2015-4271

American Academy of Pediatrics Section on Hospice and Palliative Medicine and Committee on Hospital Care. (2013). Pediatric palliative care and hospice care commitments, guidelines, and recommendations. *Pediatrics, 132*(5), 966–972. doi:10.1542/peds.2013-2731

Anand, K. J. S., & The International Evidence-Based Group for Neonatal Pain. (2001). Consensus statement for the prevention and management of pain in the newborn. *Archives of Pediatrics and Adolescent Medicine, 155*(2), 173–180. doi:10.1001/archpedi.155.2.173

Anand, K. J. S. (2007). Pharmacological approaches to the management of pain in the neonatal intensive care unit (Research Support, N. I. H., Extramural Review). *Journal of Perinatology, 27*(Suppl. 1), S4–S11. doi:10.1038/sj.jp.7211712

Anand, K. J. S. (2017). Defining pain in newborns: Need for a uniform taxonomy? *Acta Paediatrica, 106*(9), 1438–1444. doi:10.1111/apa.13936

Anand, K. J. S. (2018). Prevention and treatment of neonatal pain. In M. S. Kim (Ed.), *UpToDate*. Retrieved from https://www.uptodate.com/contents/prevention-and-treatment-of-neonatal-pain

Anand, K. J. S., Barton, B. A., McIntosh, N., Lagercrantz, H., Pelausa, E., Young, T. E., & Vasa, R. (1999). Analgesia and sedation in preterm neonates who require ventilatory support: Results from the NOPAIN trial. *Archives of Pediatrics and Adolescent Medicine, 153*(4), 331–338. doi:10.1001/archpedi.153.4.331

Anand, K. J. S., & Craig, K. D. (1996). New perspectives on the definition of pain (Editorial review). *Pain, 67*(1), 3–6; discussion 209–211. doi:10.1016/0304-3959(96)03135-1

Anand, K. J. S., Hall, R. W., Desai, N., Shephard, B., Bergqvist, L. L., Young, T. E., & Group, N. T. I. (2004). Effects of morphine analgesia in ventilated preterm neonates: Primary outcomes from the NEOPAIN randomized trial (Clinical Trial Multicenter Study Randomized Controlled Trial Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P. H. S.). *Lancet, 363*(9422), 1673–1682. doi:10.1016/S0140-6736(04)16251-X

Anand, K. J. S., Johnston, C. C., Oberlander, T. F., Taddio, A., Lehr, V. T., & Walco, G. A. (2005). Analgesia and local anesthesia during invasive procedures in the neonate (Research Support, N. I. H., Extramural Research Support, U.S. Gov't, Non-P. H. S. Research Support, U.S. Gov't, P. H. S. Review). *Clinical Therapeutics, 27*(6), 844–876. doi:10.1016/j.clinthera.2005.06.018

Anand, K. J. S., Menon, G., Narsinghani, U., & NcIntosh, N. (2000). Systemic analgesic therapy. In K. J. S. Anand, B. J. Stevens, & P. J. McGrath (Eds.), *Pain in neonates* (2nd ed.). Amsterdam, The Netherlands: Elsevier.

Anand, K. J. S, Willson, D. F., Berger, J., Harrison, R., Meert, K. L., Zimmerman, J., . . . Nicholson, C.; Human Development Collaborative Pediatric Critical Care Research Network. (2010). Tolerance and withdrawal from prolonged opioid use in critically ill children (Research Support, N. I. H., Extramural Review). *Pediatrics, 125*(5), e1208–e1225. doi:10.1542/peds.2009-0489

Axelin, A., Lehtonen, L., Pelander, T., & Salantera, S. (2010). Mothers' different styles of involvement in preterm infant pain care (Research Support, Non-U.S. Gov't). *Journal of Obstetric, Gynecologic, and Neonatal Nursing, 39*(4), 415–424. doi:10.1111/j.1552-6909.2010.01150.x

Axelin, A., Salantera, S., Kirjavainen, J., & Lehtonen, L. (2009). Oral glucose and parental holding preferable to opioid in pain management in preterm infants (Randomized Controlled Trial Research Support, Non-U.S. Gov't). *Clinical Journal of Pain, 25*(2), 138–145. doi:10.1097/AJP.0b013e318181ad81

Axelin, A., Salantera, S., & Lehtonen, L. (2006). Facilitated tucking by parents in pain management of preterm infants—A randomized crossover trial (Randomized Controlled Trial Research Support, Non-U.S. Gov't). *Early Human Development, 82*(4), 241–247. doi:10.1016/j.earlhumdev.2005.09.012

Barker, D. P., & Rutter, N. (1995). Exposure to invasive procedures in neonatal intensive care unit admissions. *Archives of Disease in Childhood. Fetal and Neonatal Edition, 72*(1), F47–F48. doi.org/10.1136/fn.72.1.F47

Beasley, R., Clayton, T., Crane, J., von Mutius, E., Lai, C. K., Montefort, S., & Stewart, A.; for the ISAAC Phase Three Study Group. (2008). Association between paracetamol use in infancy and childhood, and risk of asthma, rhinoconjunctivitis, and eczema in children aged 6-7 years: Analysis from Phase Three of the ISAAC programme (Research Support, Non-U.S. Gov't). *Lancet, 372*(9643), 1039–1048. doi:10.1016/S0140-6736(08)61445-2

Belda, S., Pallas, C. R., De la Cruz, J., & Tejada, P. (2004). Screening for retinopathy of prematurity: Is it painful? *Biology of the Neonate, 86*(3), 195–200. doi:10.1159/000079542

Bellu, R., de Waal, K., & Zanini, R. (2010). Opioids for neonates receiving mechanical ventilation: A systematic review and meta-analysis (Meta-analysis review). *Archives of Disease in Childhood. Fetal and Neonatal Edition, 95*(4), F241–F251. doi:10.1136/adc.2008.150318

Bildner, J., & Krechel, S. W. (1996). Increasing staff nurse awareness of postoperative pain management in the NICU. *Neonatal Network, 15*(1), 11–16.

Blass, E. M. (1994). Behavioral and physiological consequences of suckling in rat and human newborns (Review). *Acta Paediatrica Supplement, 83*(s397), 71–76. doi:10.1111/j.1651-2227.1994.tb13268.x

Blass, E. M., Fitzgerald, E., & Kehoe, P. (1987). Interactions between sucrose, pain and isolation distress (Research Support, U.S. Gov't, P. H. S.). *Pharmacology, Biochemistry and Behavior, 26*(3), 483–489. doi:10.1016/0091-3057(87)90153-5

Brummelte, S., Grunau, R. E., Chau, V., Poskitt, K. J., Brant, R., Vinall, J., . . . Miller, S. P. (2012). Procedural pain and brain development in premature newborns (Comparative Study Research Support, Non-U.S. Gov't). *Annals of Neurology, 71*(3), 385–396. doi:10.1002/ana.22267

Campos, R. G. (1989). Soothing pain-elicited distress in infants with swaddling and pacifiers (Research Support, U.S. Gov't, P. H. S.). *Child Development, 60*(4), 781–792. doi:10.2307/1131018

Carbajal, R., Gall, O., & Annequin, D. (2004). Pain management in neonates (Review). *Expert Review of Neurotherapeutics, 4*(3), 491–505. doi:10.1586/14737175.4.3.491

Carbajal, R., Lenclen, R., Jugie, M., Paupe, A., Barton, B. A., & Anand, K. J. (2005). Morphine does not provide adequate analgesia for acute procedural pain among preterm neonates (Clinical Trial Comparative Study Multicenter Study Randomized Controlled Trial Research Support, N. I. H., Extramural Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P. H. S.). *Pediatrics, 115*(6), 1494–1500. doi:10.1542/peds.2004-1425

Carbajal, R., Rousset, A., Danan, C., Coquery, S., Nolent, P., Ducrocq, S., . . . Breart, G. (2008). Epidemiology and treatment of painful procedures in neonates in intensive care units. *Journal of the American Medical Association, 300*(1), 60–70. doi:10.1001/jama.300.1.60

Carter, B. S., & Brunkhorst, J. (2017). Neonatal pain management. *Seminars in Perinatology, 41*(2), 111–116. doi:10.1053/j.semperi.2016.11.001

Carter, B. S., & Jones, P. M. (2013). Evidence-based comfort care for neonates towards the end of life. *Seminars in Fetal and Neonatal Medicine, 18*(2), 88–92. doi:10.1016/j.siny.2012.10.012

Cignacco, E. L., Sellam, G., Stoffel, L., Gerull, R., Nelle, M., Anand, K. J., & Engberg, S. (2012). Oral sucrose and "facilitated tucking" for repeated pain relief in preterms: A randomized controlled trial. *Pediatrics, 129*(2), 299–308. doi:10.1542/peds.2011-1879

Committee on Fetus and Newborn and Section on Anesthesiology and Pain Medicine. (2016). Prevention and management of procedural pain in the neonate: An update. *Pediatrics, 137*(2), e20154271. doi:10.1542/peds.2015-4271

Committee on Palliative and End-of-Life Care for Children and Their Families, Board on Health Sciences Policy, & Institute of Medicine. (2003). *When children die: Improving palliative and end-of-life care for children and their families*. Washington, DC: National Academies Press.

Currie, E. R., Christian, B. J., Hinds, P. S., Perna, S. J., Robinson, C., Day, S., & Meneses, K. (2016). parent perspectives of neonatal intensive care at the end-of-life. *Journal of Pediatric Nursing, 31*(5), 478–489. doi:10.1016/j.pedn.2016.03.023

Dominguez, K. D., Lomako, D. M., Katz, R. W., & Kelly, H. W. (2003). Opioid withdrawal in critically ill neonates (Clinical Trial Research Support, U.S. Gov't, P. H. S.). *Annals of Pharmacotherapy, 37*(4), 473–477. doi:10.1345/aph.1C324

Ducharme, C., Carnevale, F. A., Clermont, M. S., & Shea, S. (2005). A prospective study of adverse reactions to the weaning of opioids and benzodiazepines among critically ill children (Evaluation studies). *Intensive and Critical Care Nursing, 21*(3), 179–186. doi:10.1016/j.iccn.2004.09.003

Duhn, L. J., & Medves, J. M. (2004). A systematic integrative review of infant pain assessment tools. *Advances in Neonatal Care, 4*(3), 126–140. doi:10.1016/j.adnc.2004.04.005

Eichenfield, L. F., Funk, A., Fallon-Friedlander, S., & Cunningham, B. B. (2002). A clinical study to evaluate the efficacy of ELA-Max (4% liposomal lidocaine) as compared with eutectic mixture of local anesthetics cream for pain reduction of venipuncture in children (Clinical Trial Comparative Study Randomized Controlled Trial Research Support, Non-U.S. Gov't). *Pediatrics, 109*(6), 1093–1099. doi:10.1542/peds.109.6.1093

Field, T. (2017). Preterm newborn pain research review. *Infant Behavior and Development, 49*, 141–150. doi:10.1016/j.infbeh.2017.09.002

Fitzgerald, M., & Howard, R. F. (2003). The neurobiologic basis of pediatric pain. In N. L. Schechter, C. B. Berde, & M. Yaster (Eds.), *Pain in infants, children, and adolescents* (2nd ed.). Philadelphia, PA: Lippincott Williams & Wilkins.

Fortney, C. A., & Steward, D. K. (2014). A new framework to evaluate the quality of a neonatal death. *Death Studies, 38*(5), 294–301. doi:10.1080/07481187.2012.742475

Franck, L. S., Allen, A., Cox, S., & Winter, I. (2005). Parents' views about infant pain in neonatal intensive care. *Clinical Journal of Pain, 21*(2), 133–139. doi:10.1097/00002508-200503000-00004

Franck, L. S., Greenberg, C. S., & Stevens, B. (2000). Pain assessment in infants and children. *Pediatric Clinics of North America, 47*(3), 487–512. doi:10.1016/S0031-3955(05)70222-4

Franck, L. S., Oulton, K., & Bruce, E. (2012). Parental involvement in neonatal pain management: An empirical and conceptual update. *Journal of Nursing Scholarship, 44*(1), 45–54. doi:10.1111/j.1547-5069.2011.01434.x

Franck, L. S., Vilardi, J., Durand, D., & Powers, R. (1998). Opioid withdrawal in neonates after continuous infusions of morphine or fentanyl during extracorporeal membrane oxygenation (Comparative study). *American Journal of Critical Care, 7*(5), 364–369. Retrieved from http://ajcc.aacnjournals.org/content/7/5/364.abstract

Gale, G., Franck, L. S., Kools, S., & Lynch, M. (2004). Parents' perceptions of their infant's pain experience in the NICU. *International Journal of Nursing Studies, 41*(1), 51–58. doi:10.1016/S0020-7489(03)00096-8

Gibbins, S., & Stevens, B. (2003). The influence of gestational age on the efficacy and short-term safety of sucrose for procedural pain relief (Clinical Trial Randomized Controlled Trial Research Support, Non-U.S. Gov't). *Advances in Neonatal Care, 3*(5), 241–249. doi:10.1053/S1536-0903(03)00169-3

Gibbins, S., Stevens, B., Hodnett, E., Pinelli, J., Ohlsson, A., & Darlington, G. (2002). Efficacy and safety of sucrose for procedural pain relief in preterm and term neonates (Clinical trial randomized controlled trial). *Nursing Research, 51*(6), 375–382. doi:10.1097/00006199-200211000-00005

Giordano, V., Deindl, P., Kuttner, S., Waldhor, T., Berger, A., & Olischar, M. (2014). The Neonatal Pain, Agitation and Sedation Scale reliably detected oversedation but failed to differentiate between other sedation levels. *Acta Paediatrica, 103*(12), e515-521. doi:10.1111/apa.12770

Goldschneider, K. R., & Anand, K. S. (2003). Long-term consequences of pain in neonates. In N. L. Schechter, C. B. Berde, & M. Yaster (Eds.), *Pain in infants, children, and adolescents* (2nd ed.). Philadelphia, PA: Lippincott Williams & Wilkins.

Grunau, R., & Craig, K. D. (1987). Pain expression in neonates: Facial action and cry (Research Support, Non-U. S. Gov't). *Pain, 28*(3), 395–410. doi:10.1016/0304-3959(87)90073-X

Grossman, M. R., Berkwitt, A. K., Osborn, R. R., Xu, Y., Esserman, D. A., Shapiro, E. D., & Bizzarro, M. J. (2017). An initiative to improve the quality of care of infants with neonatal abstinence syndrome. *Pediatrics, 139*(6), e20163360. doi:10.1542/peds.2016-3360

Grunau, R., Holsti, L., & Peters, J. W. (2006). Long-term consequences of pain in human neonates (Research Support, N. I. H., Extramural Research Support, Non-U.S. Gov't Review). *Seminars in Fetal and Neonatal Medicine, 11*(4), 268–275. doi:10.1016/j.siny.2006.02.007

Grunau, R., Whitfield, M. F., & Fay, T. B. (2004). Psychosocial and academic characteristics of extremely low birth weight (≤800 g) adolescents who are free of major impairment compared with term-born control subjects (Research support, Non-U.S. Gov't). *Pediatrics, 114*(6), e725–e732. doi:10.1542/peds.2004-0932

Grunau, R., Whitfield, M. F., & Petrie, J. H. (1994). Pain sensitivity and temperament in extremely low-birth-weight premature

toddlers and preterm and full-term controls. *Pain, 58*(3), 341–346. doi:10.1016/0304-3959(94)90128-7

Hall, E. S., Rice, W. R., Folger, A. T., & Wexelblatt, S. L. (2018). Comparison of neonatal abstinence syndrome treatment with sublingual buprenorphine versus conventional opioids. *American Journal of Perinatology, 35*(4), 405–412. doi:10.1055/s-0037-1608634

Hall, R. W., & Anand, K. J. (2014). Pain management in newborns. *Clinics in Perinatology, 41*(4), 895-924. doi:10.1016/j.clp.2014.08.010

Hartley, K. A., Miller, C. S., & Gephart, S. M. (2015). Facilitated tucking to reduce pain in neonates: Evidence for best practice. *Advances in Neonatal Care, 15*(3), 201–208. doi:10.1097/ANC.0000000000000193

Haug, S., Farooqi, S., Wilson, C. G., Hopper, A., Oei, G., & Carter, B. (2018). Survey on neonatal end-of-life comfort care guidelines across America. *Journal of Pain and Symptom Management, 55*(3), 979–984. e2. doi:10.1016/j.jpainsymman.2017.10.023

Herrington, C. J., Olomu, I. N., & Geller, S. M. (2004). Salivary cortisol as indicators of pain in preterm infants: A pilot study (Research Support, Non-U.S. Gov't Validation Studies). *Clinical Nursing Research, 13*(1), 53–68. doi:10.1177/1054773803259665

Hillman, B. A., Tabrizi, M. N., Gauda, E. B., Carson, K. A., & Aucott, S. W. (2015). The neonatal pain, agitation and sedation scale and the bedside nurse's assessment of neonates. *Journal of Perinatology, 35*(2), 128–131. doi:10.1038/jp.2014.154

Holsti, L., Grunau, R. E., Oberlander, T. F., & Whitfield, M. F. (2004). Specific newborn individualized developmental care and assessment program movements are associated with acute pain in preterm infants in the neonatal intensive care unit (Research Support, Non-U.S. Gov't Research Support, U. S. Gov't, P. H. S.). *Pediatrics, 114*(1), 65–72. doi:10.1542/peds.114.1.65

Hsu, D. C. (2018). Clinical use of topical anesthetics in children. In J. F. Wiley, 2nd (Ed.), *UpToDate*. Retrieved from https://www.uptodate.com/contents/clinical-use-of-topical-anesthetics-in-children

Hudak, M. L., & Tan, R. C.; Committee on Drugs and the Committee on Fetus and Newborn, & American Academy of Pediatrics. (2012). Neonatal drug withdrawal (Practice guideline). *Pediatrics, 129*(2), e540–e560. doi:10.1542/peds.2011-3212

Hummel, P., Puchalski, M., Creech, S. D., & Weiss, M. G. (2008). Clinical reliability and validity of the N-PASS: Neonatal pain, agitation and sedation scale with prolonged pain (Research Support, Non-U.S. Gov't Validation Studies). *Journal of Perinatology, 28*(1), 55–60. doi:10.1038/sj.jp.7211861

Johnston, C. C., Barrington, K. J., Taddio, A., Carbajal, R., & Filion, F. (2011). Pain in Canadian NICUs: Have we improved over the past 12 years? (Research Support, Non-U.S. Gov't). *Clinical Journal of Pain, 27*(3), 225–232. doi:10.1097/AJP.0b013e3181fe14cf

Johnston, C. C., Campbell-Yeo, M., Disher, T., Benoit, B., Fernandes, A., Streiner, D., . . . Zee, R. (2017). Skin-to-skin care for procedural pain in neonates. *Cochrane Database of Systematic Reviews*, (2), CD008435. doi:10.1002/14651858.CD008435.pub3

Johnston, C. C., Filion, F., Campbell-Yeo, M., Goulet, C., Bell, L., McNaughton, K., . . . Walker, C. D. (2008). Kangaroo mother care diminishes pain from heel lance in very preterm neonates: A crossover trial. *BMC Pediatrics, 8*, 13. doi:10.1186/1471-2431-8-13

Johnston, C. C., Filion, F., Snider, L., Majnemer, A., Limperopoulos, C., Walker, C. D., & Boyer, K. (2002). Routine sucrose analgesia during the first week of life in neonates younger than 31 weeks' postconceptional age (Clinical Trial Multicenter Study Randomized Controlled Trial Research Support, Non-U.S. Gov't). *Pediatrics, 110*(3), 523–528. doi:10.1542/peds.110.3.523

Johnston, C. C., & Stevens, B. J. (1996). Experience in a neonatal intensive care unit affects pain response. *Pediatrics, 98*(5), 925–930. Retrieved from https://pediatrics.aappublications.org/content/98/5/925

Johnston, C. C., Stevens, B. J., Pinelli, J., Gibbins, S., Filion, F., Jack, A., . . . Veilleux, A. (2003). Kangaroo care is effective in diminishing pain response in preterm neonates. *Archives of Pediatrics and Adolescent Medicine, 157*(11), 1084–1088. doi:10.1001/archpedi.157.11.1084

Kaur, G., Gupta, P., & Kumar, A. (2003). A randomized trial of eutectic mixture of local anesthetics during lumbar puncture in newborns (Clinical Trial Randomized Controlled Trial). *Archives of Pediatrics and Adolescent Medicine, 157*(11), 1065–1070. doi:10.1001/archpedi.157.11.1065

Kleiber, C., Sorenson, M., Whiteside, K., Gronstal, B. A., & Tannous, R. (2002). Topical anesthetics for intravenous insertion in children: A randomized equivalency study (Clinical Trial Comparative Study Randomized Controlled Trial Research Support, U.S. Gov't, P. H. S.). *Pediatrics, 110*(4), 758–761. doi:10.1542/peds.110.4.758

Kocherlakota, P. (2014). Neonatal abstinence syndrome. *Pediatrics, 134*(2), e547–e561. doi:10.1542/peds.2013-3524

Koh, J. L., Harrison, D., Myers, R., Dembinski, R., Turner, H., & McGraw, T. (2004). A randomized, double-blind comparison study of EMLA® and ELA-Max® for topical anesthesia in children undergoing intravenous insertion (Clinical trial comparative study randomized controlled trial). *Paediatric Anaesthesia, 14*(12), 977–982. doi:10.1111/j.1460-9592.2004.01381.x

Kraft, W. K., Adeniyi-Jones, S. C., Chervoneva, I., Greenspan, J. S., Abatemarco, D., Kaltenbach, K., & Ehrlich, M. E. (2017). Buprenorphine for the treatment of the neonatal abstinence syndrome. *New England Journal of Medicine, 376*(24), 2341–2348. doi:10.1056/NEJMoa1614835

Krechel, S. W., & Bildner, J. (1995). CRIES: A new neonatal postoperative pain measurement score. Initial testing of validity and reliability. *Paediatric Anaesthesia, 5*(1), 53–61. doi:10.1111/j.1460-9592.1995.tb00242.x

Lander, J. A., Weltman, B. J., & So, S. S. (2006). EMLA and amethocaine for reduction of children's pain associated with needle insertion. *Cochrane Database of Systematic Reviews,* (3), *CD004236*. doi:10.1002/14651858.CD004236.pub2

Lawrence, J., Alcock, D., McGrath, P., Kay, J., MacMurray, S. B., & Dulberg, C. (1993). The development of a tool to assess neonatal pain. *Neonatal Network, 12*(6), 59–66.

Lehr, V. T., Cepeda, E., Frattarelli, D. A., Thomas, R., LaMothe, J., & Aranda, J. V. (2005). Lidocaine 4% cream compared with lidocaine 2.5% and prilocaine 2.5% or dorsal penile block for circumcision (Comparative Study Randomized Controlled Trial Research Support, Non-U.S. Gov't). *American Journal of Perinatology, 22*(5), 231–237. doi:10.1055/s-2005-871655

Lexicomp. (2018, May). *Pediatric and neonatal Lexi-drugs online*. Hudson, OH: Wolters Kluwer Clinical Drug Information.

Liaw, J. J., Yang, L., Ti, Y., Blackburn, S. T., Chang, Y. C., & Sun, L. W. (2010). Non-nutritive sucking relieves pain for preterm infants during heel stick procedures in Taiwan (Research Support, Non-U.S. Gov't). *Journal of Clinical Nursing, 19*(19/20), 2741–2751. doi:10.1111/j.1365-2702.2010.03300.x

Liaw, J. J., Zeng, W. P., Yang, L., Yuh, Y. S., Yin, T., & Yang, M. H. (2011). Nonnutritive sucking and oral sucrose relieve neonatal pain during intramuscular injection of hepatitis vaccine (Comparative study randomized controlled trial). *Journal of Pain and Symptom Management, 42*(6), 918–930. doi:10.1016/j.jpainsymman.2011.02.016

Magnus, M. C., Karlstad, Ø., Håberg, S. E., Nafstad, P., Smith, G. D., & Nystad, W. (2016). Prenatal and infant paracetamol exposure and development of asthma: The Norwegian mother and child cohort study. *International Journal of Epidemiology, 45*(2), 512–522. doi.org/10.1093/ije/dyv366

Marfurt-Russenberger, K., Axelin, A., Kesselring, A., Franck, L. S., & Cignacco, E. (2016). The experiences of professionals regarding involvement of parents in neonatal pain management. *Journal of Obstetric, Gynecologic, and Neonatal Nursing, 45*(5), 671–683. doi:10.1016/j.jogn.2016.04.011

Mathai, S. S., Naresh, A., & Sahu, S. (2011). Behavioral response to pain in drowsy and sleeping neonates: A randomized control study (Randomized controlled trial). *Indian Pediatrics, 48*(5), 390–392. doi:10.1007/s13312-011-0082-1

McNair, C., Ballantyne, M., Dionne, K., Stephens, D., & Stevens, B. (2004). Postoperative pain assessment in the neonatal intensive care unit (Clinical Trial Comparative Study Randomized Controlled Trial

Research Support, Non-U.S. Gov't Validation Studies). *Archives of Disease in Childhood. Fetal and Neonatal Edition, 89*(6), F537–F541. doi:10.1136/adc.2003.032961

Mele, C. (2018). The use of near infrared spectroscopy to assess infant pain. *Journal of Pediatric Nursing, 39*, 85–88. doi:10.1016/j.pedn.2017.12.009

Menon, G., Anand, K. J., & McIntosh, N. (1998). Practical approach to analgesia and sedation in the neonatal intensive care unit (Review). *Seminars in Perinatology, 22*(5), 417–424. doi:10.1016/S0146-0005(98)80057-8

Merskey, H. (1979). Pain terms: A list with definitions and notes on usage. Recommended by the IASP Subcommittee on Taxonomy. *Pain, 6*(3), 249.

Miles, M. S., & Holditch-Davis, D. (1997). Parenting the prematurely born child: Pathways of influence (Research Support, U.S. Gov't, P. H. S. Review). *Seminars in Perinatology, 21*(3), 254–266. doi:10.1016/S0146-0005(97)80067-5

National Association of Neonatal Nurses. (2012). *Newborn pain assessment and management: Guideline for practice*. Des Plaines, IL: Author.

Ng, E., Taddio, A., & Ohlsson, A. (2017). Intravenous midazolam infusion for sedation of infants in the neonatal intensive care unit. *Cochrane Database of Systematic Reviews*, (1), CD002052. doi:10.1002/14651858.CD002052.pub3

Obeidat, H., Kahalaf, I., Callister, L. C., & Froelicher, E. S. (2009). Use of facilitated tucking for nonpharmacological pain management in preterm infants: A systematic review (Review). *Journal of Perinatal and Neonatal Nursing, 23*(4), 372–377. doi:10.1097/JPN.0b013e3181bdcf77

O'Brien, L., Taddio, A., Lyszkiewicz, D. A., & Koren, G. (2005). A critical review of the topical local anesthetic amethocaine (Ametop™) for pediatric pain. *Paediatric Drugs, 7*(1), 41–54. doi:10.2165/00148581-200507010-00004

Ohlsson, A., & Shah, P. S. (2016). Paracetamol (acetaminophen) for prevention or treatment of pain in newborns. *Cochrane Database of Systematic Reviews*, (10), CD011219. doi:10.1002/14651858.CD011219.pub3

Palomaa, A. K., Korhonen, A., & Polkki, T. (2016). Factors influencing parental participation in neonatal pain alleviation. *Journal of Pediatric Nursing, 31*(5), 519–527. doi:10.1016/j.pedn.2016.05.004

Partridge, J. C., & Wall, S. N. (1997). Analgesia for dying infants whose life support is withdrawn or withheld (Research Support, U.S. Gov't, P. H. S.). *Pediatrics, 99*(1), 76–79. doi:10.1542/peds.99.1.76

Pillai Riddell, R., Racine, N., Turcotte, K., Uman, L., Horton, R., Din Osmun, L., . . . Lisi, D. (2011). Nonpharmacological management of procedural pain in infants and young children: An abridged Cochrane review (Research Support, Non-U.S. Gov't Review). *Pain Research and Management, 16*(5), 321–330. doi:10.1155/2011/489286

Pinheiro, J. M., Furdon, S., & Ochoa, L. F. (1993). Role of local anesthesia during lumbar puncture in neonates. *Pediatrics, 91*(2), 379–382. Retrieved from https://pediatrics.aappublications.org/content/91/2/379

Porter, F. L., Wolf, C. M., & Miller, J. P. (1998). The effect of handling and immobilization on the response to acute pain in newborn infants (Clinical Trial Randomized Controlled Trial Research Support, U.S. Gov't, P. H. S.). *Pediatrics, 102*(6), 1383–1389. doi:10.1542/peds.102.6.1383

Prymula, R., Siegrist, C. A., Chlibek, R., Zemlickova, H., Vackova, M., Smetana, J., . . . Schuerman, L. (2009). Effect of prophylactic paracetamol administration at time of vaccination on febrile reactions and antibody responses in children: Two open-label, randomised controlled trials (Clinical Trial, Phase III Multicenter Study Randomized Controlled Trial Research Support, Non-U.S. Gov't). *Lancet, 374*(9698), 1339–1350. doi:10.1016/S0140-6736(09)61208-3

Rao, R., Sampers, J. S., Kronsberg, S. S., Brown, J. V., Desai, N. S., & Anand, K. J. (2007). Neurobehavior of preterm infants at 36 weeks postconception as a function of morphine analgesia (Randomized Controlled Trial Research Support, N. I. H., Extramural Research Support, Non-U.S. Gov't). *American Journal of Perinatology, 24*(9), 511–517. doi:10.1055/s-2007-986675

Regen, R., & Whitehill, J. (2012). Drug considerations in circumcision. *U.S. Pharmacist, 27*(3), HS-2-5. Retrieved from https://www.uspharmacist.com/article/drug-therapy-considerations-in-circumcision

Rouss, K., Gerber, A., Albisetti, M., Hug, M., & Bernet, V. (2007). Long-term subcutaneous morphine administration after surgery in newborns. *Journal of Perinatal Medicine, 35*(1), 79–81. doi:10.1515/JPM.2007.013

Roze, J. C., Denizot, S., Carbajal, R., Ancel, P. Y., Kaminski, M., Arnaud, C., . . . Breart, G. (2008). Prolonged sedation and/or analgesia and 5-year neurodevelopment outcome in very preterm infants: Results from the EPIPAGE cohort (Comparative study). *Archives of Pediatrics and Adolescent Medicine, 162*(8), 728–733. doi:10.1001/archpedi.162.8.728

Saarenmaa, E., Huttunen, P., Leppaluoto, J., Meretoja, O., & Fellman, V. (1999). Advantages of fentanyl over morphine in analgesia for ventilated newborn infants after birth: A randomized trial (Clinical Trial Comparative Study Randomized Controlled Trial). *Journal of Pediatrics, 134*(2), 144–150. doi:10.1016/S0022-3476(99)70407-5

Sanlorenzo, L. A., Stark, A. R., & Patrick, S. W. (2018). Neonatal abstinence syndrome: An update. *Current Opinion in Pediatrics, 30*(2):182–186. doi:10.1097/MOP.0000000000000589

Sethna, N. F., & Koh, J. L. (2000). Regional anesthesia and analgesia. In K. J. S. Anand, B. J. Stevens, & P. J. McGrath (Eds.), *Pain in neonates* (2nd ed.). Amsterdam, The Netherlands: Elsevier.

Sheehan, W. J., Mauger, D. T., Paul, I. M., Moy, J. N., Boehmer, S. J., Szefler, S. J., . . . AsthmaNet, N. N. (2016). Acetaminophen versus ibuprofen in young children with mild persistent asthma. *The New England Journal of Medicine, 375*(7), 619–630. doi:10.1056/NEJMoa1515990

Simons, S. H., & Anand, K. J. (2006). Pain control: Opioid dosing, population kinetics and side-effects. *Seminars in Fetal and Neonatal Medicine, 11*(4), 260–267. doi:10.1016/j.siny.2006.02.008

Simons, S. H., & Tibboel, D. (2006). Pain perception development and maturation (Review). *Seminars in Fetal and Neonatal Medicine, 11*(4), 227–231. doi:10.1016/j.siny.2006.02.010

Simons, S. H., van Dijk, M., Anand, K. S., Roofthooft, D., van Lingen, R. A., & Tibboel, D. (2003). Do we still hurt newborn babies? A prospective study of procedural pain and analgesia in neonates. *Archives of Pediatrics and Adolescent Medicine, 157*(11), 1058–1064. doi:10.1001/archpedi.157.11.1058 157/11/1058

Simons, S. H., van Dijk, M., van Lingen, R. A., Roofthooft, D., Duivenvoorden, H. J., Jongeneel, N., & Tibboel, D. (2003). Routine morphine infusion in preterm newborns who received ventilatory support: A randomized controlled trial. *Journal of the American Medical Association, 290*(18), 2419–2427. doi:10.1001/jama.290.18.2419 290/18/2419

Spruill, C. T., & LaBrecque, M. A. (2017). Preventing and treating pain and stress among infants in the newborn intensive care unit. In E. C. Eichenwald, A. R. Hansen, C. R. Martin, & A. R. Stark (Eds.), *Cloherty and Stark's manual of neonatal care* (8th ed., pp. 1022–1042). Philadelphia, PA: Wolters Kluwer.

Stevens, B. J., Gibbins, S., Yamada, J., Dionne, K., Lee, G., Johnston, C., . . . Taddio, A. (2014). The premature infant pain profile-revised (PIPP-R): Initial validation and feasibility. *The Clinical Journal of Pain, 30*(3), 238–243. doi:10.1097/AJP.0b013e3182906aed

Stevens, B. J., Johnston, C., Franck, L., Petryshen, P., Jack, A., & Foster, G. (1999). The efficacy of developmentally sensitive interventions and sucrose for relieving procedural pain in very low birth weight neonates (Clinical Trial Comparative Study Multicenter Study Randomized Controlled Trial Research Support, Non-U. S. Gov't Research Support, U.S. Gov't, P. H. S.). *Nursing Research, 48*(1), 35–43. doi:10.1097/00006199-199901000-00006

Stevens, B. J., Johnston, C. C., & Horton, L. (1994). Factors that influence the behavioral pain responses of premature infants (Clinical Trial Research Support, Non-U.S. Gov't). *Pain, 59*(1), 101–109. doi:10.1016/0304-3959(94)90053-1

Stevens, B. J., Johnston, C., Petryshen, P., & Taddio, A. (1996). Premature infant pain profile: Development and initial validation (Clinical Trial Research Support, Non-U.S. Gov't). *Clinical Journal Pain, 12*(1), 13–22. doi:10.1097/00002508-199603000-00004

Stevens, B. J., Johnston, C., Taddio, A., Gibbins, S., & Yamada, J. (2010). The premature infant pain profile: Evaluation 13 years after development (Research Support, Non-U.S. Gov't Review). *Clinical Journal Pain, 26*(9), 813–830. doi:10.1097/AJP.0b013e3181ed1070

Stevens, B. J. , Yamada, J., Beyene, J., Gibbins, S., Petryshen, P., Stinson, J., & Narciso, J. (2005). Consistent management of repeated procedural pain with sucrose in preterm neonates: Is it effective and safe for repeated use over time? *Clinical Journal Pain, 21*(6), 543–548. doi:10.1097/01.ajp.0000149802.46864.e2

Stevens, B. J., Yamada, J., Ohlsson, A., Haliburton, S., & Shorkey, A. (2016). Sucrose for analgesia in newborn infants undergoing painful procedures. *Cochrane Database of Systematic Reviews*, (7), CD001069. doi:10.1002/14651858.CD001069.pub5

Suraseranivongse, S., Kaosaard, R., Intakong, P., Pornsiriprasert, S., Karnchana, Y., Kaopinpruck, J., & Sangjeen, K. (2006). A comparison of postoperative pain scales in neonates (Comparative Study Research Support, Non-U.S. Gov't Validation Studies). *British Journal of Anaesthesia, 97*(4), 540–544. doi:10.1093/bja/ael184

Taddio, A., Goldbach, M., Ipp, M., Stevens, B., & Koren, G. (1995). Effect of neonatal circumcision on pain responses during vaccination in boys (Research Support, Non-U.S. Gov't). *The Lancet, 345*(8945), 291–292. doi:10.1016/S0140-6736(95)90278-3

Taddio, A., Katz, J., Ilersich, A. L., & Koren, G. (1997). Effect of neonatal circumcision on pain response during subsequent routine vaccination (Clinical Trial Randomized Controlled Trial Research Support, Non-U.S. Gov't). *Lancet, 349*(9052), 599–603. doi:10.1016/S0140-6736(96)10316-0

Taddio, A., Lee, C., Yip, A., Parvez, B., McNamara, P. J., & Shah, V. (2006). Intravenous morphine and topical tetracaine for treatment of pain in [corrected] neonates undergoing central line placement (Randomized Controlled Trial Research Support, Non-U.S. Gov't). *Journal of the American Medical Association, 295*(7), 793–800. doi:10.1001/jama.295.7.793

Taddio, A., Shennan, A. T., Stevens, B., Leeder, J. S., & Koren, G. (1995). Safety of lidocaine-prilocaine cream in the treatment of preterm neonates. *Journal of Pediatrics, 127*(6), 1002–1005. doi:10.1016/S0022-3476(95)70050-1

Valeur, K. S., Hertel, S. A., Lundstrøm K. E., & Holst, H. (2018). The cumulative daily tolerance levels of potentially toxic excipients ethanol and propylene glycol are commonly exceeded in neonates and infants. *Basic and Clinical Pharmacology and Toxicology, 122*(5), 523–530. doi:10.1111/bcpt.12950

van Ganzewinkel, C. J., Anand, K. J., Kramer, B. W., & Andriessen, P. (2014). Chronic pain in the newborn: Toward a definition. *The Clinical Journal of Pain, 30*(11), 970–977. doi:10.1097/AJP.0000000000000056

Walden, M. (2001). *Pain assessment and management: Guideline for practice*. Glenview, IL: National Association of Neonatal Nurses.

Walden, M., Penticuff, J. H., Stevens, B., Lotas, M. J., Kozinetz, C. A., Clark, A., . . . Avant, K. C. (2001). Maturational changes in physiologic and behavioral responses of preterm neonates to pain. *Advances in Neonatal Care, 1*(2), 94. doi:10.1053/adnc.2001.29593

Walden, M., Sudia-Robinson, T., & Carrier, C. (2001). Comfort care for infants in the neonatal intensive care unit at end of life. *Newborn and Infant Nursing Reviews, 1(2)*, 97–105. doi:10.1053/nbin.2001.25436

Walker, S. M. (2013). Biological and neurodevelopmental implications of neonatal pain. *Clinics in Perinatology, 40*(3), 471–491. doi:10.1016/j.clp.2013.05.002

Wallace, H., & Jones, T. (2017). Managing procedural pain on the neonatal unit: Do inconsistencies still exist in practice? *Journal of Neonatal Nursing, 23*(3),119–126. doi.org/10.1016/j.jnn.2016.10.004

Walter-Nicolet, E., Annequin, D., Biran, V., Mitanchez, D., & Tourniaire, B. (2010). Pain management in newborns: From prevention to treatment (Review). *Paediatric Drugs, 12*(6), 353–365. doi:10.2165/11318900-000000000-00000

Whitfield, M. F., Grunau, R. V., & Holsti, L. (1997). Extremely premature (≤ 800 g) schoolchildren: Multiple areas of hidden disability. *Archives of Disease in Childhood. Fetal and Neonatal Edition, 77*(2), F85–F90. doi:10.1136/fn.77.2.F85

Willis, D. M., Chabot, J., Radde, I. C., & Chance, G. W. (1977). Unsuspected hyperosmolality of oral solutions contributing to necrotizing enterocolitis in very-low-birth-weight infants. *Pediatrics, 60*(4), 535–538. Retrieved from https://pediatrics.aappublications.org/content/60/4/535

Wysocki, J., Center, K. J., Brzostek, J., Majda-Stanislawka, E., Szymanski, H., Szenborn, L., . . . Gurtmann, A. (2017). A randomized study of fever prophylaxis and the immunogenicity of routine pediatric vaccinations. *Vaccine, 35*(15), 1926–1935. doi:10.1016/j.vaccine.2017.02.035

Young, T. E., & Mangum, B. (2010). *NeoFax* (23rd ed.). Montvale, NJ: Thomson Reuters and Lexicomp.

Young, T. E., & Mangum, B. (2011). *NeoFax*. (24th ed.). Montvale, NJ: Thomson Reuters.

Zuppa, A. F., Hammer, G. B., Barrett, J. S., Kenney, B. F., Kassir, N., Mouksassi, S., & Royal, M. A. (2011). Safety and population pharmacokinetic analysis of intravenous acetaminophen in neonates, infants, children, and adolescents with pain or fever. *The Journal of Pediatric Pharmacology and Therapeutics, 16*(4), 246–261. doi:10.5863/1551-6776-16.4.246

Zwicker, J. G., Miller, S. P., Grunau, R. E., Chau, V., Brant, R., Studholme, C., . . . & Tam, E. W. (2016). Smaller cerebellar growth and poorer neurodevelopmental outcomes in very preterm infants exposed to neonatal morphine. *The Journal of Pediatrics, 172,* 81–87. doi:10.1016/j.jpeds.2015.12.024

CHAPTER 24

Fetal Therapy

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INTRODUCTION

Fetal therapy includes any intervention (invasive and/or noninvasive) performed to improve the health of children by intervening before birth to correct or treat a prenatally diagnosed abnormality. These therapies include ultrasound-guided needle procedures (fetal blood sampling, intrauterine blood transfusion, shunts, balloon valvuloplasty or septostomy, and radiofrequency ablation), fetoscopic procedures (posterior urethral valves [PUVs], photocoagulation, umbilical cord occlusion, tracheal occlusion, and amniotic band release), open fetal surgery (OFS; myelomeningocele [MMC] repair, lobectomy, and teratoma resection), and *ex-utero* intrapartum treatment (EXIT; Moon-Grady et al., 2017). This chapter will provide a historical overview of fetal therapy, the importance of a multidisciplinary approach, fetal diagnoses amenable to fetal therapy, and care of the maternal–fetal dyad before, during, and after intervention.

HISTORICAL OVERVIEW

The history of fetal therapy started over three decades ago when practitioners met to discuss this emerging field. The overall goal of this meeting was to change the outcomes for diseases like hydrocephalus, obstructive uropathy, and pulmonary hypoplasia (Moon-Grady et al., 2017). Initial experiments related to fetal therapy focused on how to safely and effectively gain access to the uterus. Next, the fetal surgical approaches needed to be studied, which were initially performed on animal models, such as dogs, rabbits, primates, and lambs (Deprest et al., 2010).

In 1963, Sir William Liley made medical history when he became the first doctor to give a fetus a blood transfusion before birth (McMann, Carter, & Lantos, 2014). The significance of his achievement was not only a major advancement in the management of erythroblastosis fetalis but also the first real demonstration that the fetus is accessible to skilled diagnosis and treatment. The story of modern fetal surgery started with Dr. Harrison at the University of California, San Francisco (UCSF). In 1981, a multidisciplinary team at UCSF became the first group to clinically attempt correction of urinary tract obstruction in utero by placing a catheter into the fetal bladder to bypass the obstruction and prevent pulmonary hypoplasia or renal failure (Deprest et al., 2010). See Table 24.1 for additional fetal therapy hallmark cases.

TABLE 24.1

TIMELINE IN THE EVOLUTION OF FETAL THERAPY

Year	First	Open vs. MIS
1963	Fetal transfusion	MIS
1981	Vesicoamniotic shunt placement	MIS
1982	Fetal surgery	Open
1984	Lung lesion resection	Open
1987	Fetal thoracoamniotic shunt placement	MIS
1990	Laser ablation for TTTS	MIS
1992	Sacrococcygeal teratoma debulking	Open
1995	EXIT procedure	Open
1997	Fetoscopic repair of myelomeningocele	MIS
1997	"Fetendo" tracheal clipping for CDH	MIS
1997	Fetoscopic release of amniotic band	MIS
2001	Fetoscopic balloon tracheal occlusion for CDH	MIS

CDH, congenital diaphragmatic hernia; EXIT, *ex-utero* intrapartum therapy; MIS, minimally invasive surgery; TTTS, twin-to-twin transfusion syndrome.

Source: With permission from Graves, C. E., Harrison, M. R., & Padilla, B. E. (2017). Minimally invasive fetal surgery. *Clinics in Perinatology, 44*(4), 729–751. doi:10.1016/j.clp.2017.08.001

ETHICAL CONSIDERATIONS

Since the fetus became a patient over three decades ago, there has been an increase in overall acceptance to this ever-changing patient population. Given that fetal interventions are motivated by beneficence, ethical considerations must include maternal autonomy and decision making (American College of Obstetricians and Gynecologists [ACOG] Committee on Ethics & American Academy of Pediatrics [AAP] Committee on Bioethics, 2011; Titus & Moodley, 2012). Any fetal intervention has implications on maternal health, without actual benefit to the mother; therefore, these interventions cannot be performed without her informed consent. The goals of the treatment and any conflicting data or paucity of data should be disclosed at that time (Titus & Moodley, 2012). A thorough unbiased discussion that includes the risks and benefits to the fetus as well as the risks and benefits of obstetric and neonatal care without fetal intervention should be had at that time. Maternal risk is primarily related to the high incidence of preterm labor and its corresponding morbidity, risk of infection, and bleeding. There is an increased risk of uterine rupture after hysterotomy (Al-Refai, Ryan, & Van Mieghem, 2017), which is associated with significant maternal morbidities and mortalities that place subsequent pregnancies at risk (ACOG Committee on Ethics & AAP Committee on Bioethics, 2011).

In addition to uterine rupture, pulmonary edema after fetal intervention can be due to generous volume overload during OFS, fluid resorption after laser ablation for twin-to-twin transfusion syndrome (TTTS), or from tocolytic use especially when different classes of tocolytics are used together (Al-Refai et al., 2017). **Emergency Alert: Complications of OFS include placental abruption, chorioamnionitis, and possible need for blood transfusion.** Fertility is not affected and the miscarriage rate in subsequent pregnancies is comparable with baseline. Risks to the fetus include intrauterine demise, bleeding depending on the intervention, failed intervention requiring repeated attempts, and premature birth.

Maternal–Fetal Imaging

Ultrasonography is an essential adjunct to prenatal diagnostic procedures that has laid the groundwork for fetal therapy that is performed today. This method of imaging is used to confirm the fetal gestational age and number, malformations, fetal well-being, and aid in procedures like amniocentesis, chorionic villus sampling, and percutaneous umbilical blood sampling. In addition, it is used to determine placenta location and blood flow to the fetus. Although prenatal diagnoses are primarily made by ultrasound, ultrafast fetal MRI has been helpful in ruling out alternative diagnoses (Khalek & Johnson, 2013). Fetal MRI may be more sensitive than ultrasound due to high soft-tissue contrast (Euser, Meyers, Zaretsky, & Crombleholme, 2016). The advantages of MRI include the use of multiple planes for reconstruction and a large field of view, making the visualization of complicated anomalies easier. For the most accurate diagnosis and detailed anatomy, imaging should include the following: high-resolution 3D and 4D ultrasound, MRI, and echocardiography (Rintoul, Ades, & Adzick, 2018).

Multidisciplinary Team Approach

Quality and Safety: For maximum benefit, candidates for fetal surgery should be identified and referred before 23 weeks' gestation. This allows the multidisciplinary team to evaluate the maternal–fetal dyad and perform appropriately timed interventions. After 30 weeks' gestation, manipulation of the uterus is associated with a higher risk of premature rupture of the membranes (PROM) and preterm labor; thus, delivery of the fetus and treatment of the malformation with standard postnatal care becomes a more reasonable approach (Kiatano, 1999). When fetal therapy is the chosen treatment, the clinical case must be broken down into six phases: diagnosis, information and decision making, perioperative and postoperative care, home care and follow-up, delivery, and neonatal period. Each phase involves distinct and important nursing input and responsibilities.

Once the mother is referred to a fetal treatment center, the family is given information about the reason for the referral and the evaluation process. For many families, this is the most difficult time, and the nurse should provide appropriate and sufficient information about the process to help families cope during this stressful situation. The nurse must recognize that the family is experiencing the loss of a normal pregnancy and experiencing anxiety of an uncertain future. The diagnostic phase includes maternal evaluation, including physical examination as well as blood work. Fetal evaluation includes imaging via 3D or 4D ultrasound, ultrafast MRI, and genetic testing. The information collected during this phase will determine whether the maternal–fetal dyad is a candidate for fetal therapy. See Box 24.1 for inclusion and exclusion criteria for fetal therapy.

Given the complexity of fetal therapy, a multidisciplinary team approach is needed to care for the mother and fetus. This team should include a perinatologist, neonatologist, pediatric surgeon (cardiologist, urologist, neurosurgeon, fetal), sonographer, anesthesiologist, operating room and perinatal nurse specialists, social work, and a nurse coordinator who can serve as a liaison with the family

At the time of delivery, the multidisciplinary team for the mother includes obstetric and/or operating room nurses, certified nurse midwife, obstetrician, and anesthesiologist. For the newborn, the team includes neonatologist, surgical advance practice nurse, neonatal nurses, and neonatal respiratory therapist. These team members have advanced knowledge in fetal therapy procedures and are certified neonatal resuscitation providers (Neonatal Resuscitation Program [NRP]).

Box 24.1

CRITERIA FOR FETAL THERAPY

Maternal Exclusion Criteria

- Maternal age <18 years
- History of cervical insufficiency and/or short cervix <20 mm on transvaginal ultrasound
- Placenta previa
- Other serious maternal medical condition
- Previous spontaneous singleton delivery <37 weeks' gestation
- Maternal–fetal Rh alloimmunization
- Uterine anomaly
- Psychosocial limitations
- Inability to comply with travel and follow-up

Fetal Inclusion Criteria

- Singleton with no additional fetal anomalies related to primary diagnosis
- Normal karyotype
- Ultrasound evidence of cardiac dysfunction and/or hydrops
- Gestational age <32 weeks

Source: With permission from Khalek, N., & Johnson, M. P. (2013). Management of prenatally diagnosed lung lesions. *Seminars in Pediatric Surgery, 22*, 24–29. doi:10.1053/j.sempedsurg.2012.10.005

Procedures

One of the best-known forms of fetal therapy is transplacental passage of maternal medications, like corticosteroids, antiarrhythmic drugs, and intravenous immunoglobulins (Al-Refai et al., 2017). Steroids have been used in treating fetal conditions like congenital adrenal hyperplasia, lung maturation, and experimentally in the treatment of anti-Ro/La antibody-mediated fetal heart block (Al-Refai et al., 2017). Persistent fetal tachyarrhythmias, like supraventricular tachycardia and atrial flutter, will often lead to fetal hydrops and demise. Antiarrhythmic agents, like digoxin, flecainide, or sotalol, have been administered to healthy pregnant women without adverse cardiac events being reported for the mother. Lastly, intravenous maternal administration of immunoglobulins treats fetal alloimmune thrombocytopenia (Al-Refai et al., 2017). Although medical interventions can be performed for amenable fetal conditions, there are other conditions where surgical interventions may be needed.

Minimally invasive fetal surgery (MIFS) and procedures have become popular options due to the rise in popularity of adult laparoscopic surgery and the development of size-appropriate fetoscopic instruments. Minimally invasive procedures can be used to treat prenatal diagnoses such as congenital diaphragmatic hernia (CDH), lower urinary tract obstruction (LUTO), TTTS, intravenous fetal blood transfusion for anemia, and cardiac anomalies such as aortic stenosis (Saracoglu, Saracoglu, & Kafali, 2016; Wenstrom & Carr, 2014). As with OFS and the EXIT procedure, MIFS and procedures require an experienced, multidisciplinary team approach; many members of the team meet weekly to discuss upcoming cases and corresponding imaging (Graves et al., 2017). The minimally invasive fetal teams typically include members of the following disciplines: fetal/pediatric surgery, obstetrics, maternal–fetal medicine (MFM), anesthesia, cardiology, urology and obstetric/perinatal, operating room, and neonatal nursing.

Closed fetal procedures are performed under ultrasound guidance, employ the use of a needle or a trocar, either of which is inserted through the maternal abdominal and uterine walls, and are usually limited to one access point (Nassr, Erfani, et al., 2017). Needle-based procedures are percutaneous umbilical blood sampling, balloon valvuloplasty, shunt placement (thoracoamniotic or vesicoamniotic), and radiofrequency ablation (Hoagland & Chatterjee, 2017). Closed fetal procedures are performed under local and/or regional (epidural or spinal) anesthesia (Nassr, Erfani, et al., 2017; Wenstrom & Carr, 2014). The procedures are typically performed percutaneously; however, it can be performed via a small laparotomy giving better access to the uterus (Nassr, Erfani, et al., 2017; Wenstrom & Carr, 2014). The benefit of greater exposure to the uterus becomes important for the surgeons when the case is particularly difficult, or the fetal position needs to be changed or maintained.

The importance of real-time ultrasound imaging during minimally invasive fetal procedures cannot be underscored enough. Ultrasound is used to ensure safe entry to the uterus, as well as identify placental position, fetal position and well-being, fetal cardiac function, and umbilical artery blood flow. In the situation of an anterior placenta, curved instruments can be utilized to avoid the placenta while under ultrasound guidance (Graves et al., 2017).

The fetoscopic approach is the second mode of minimally invasive fetal procedures and is utilized for ablation of PUVs, amniotic band release, tracheal occlusion, laser photocoagulation for TTTS, and umbilical cord coagulation (Hoagland & Chatterjee, 2017). Fetoscopy is performed in a manner similar to that of the closed procedures. Real-time ultrasound guidance is used to ensure safe access to the uterine cavity and is used as an adjunct to the fetoscope to visualize the fetus and its well-being throughout the procedure (Graves et al., 2017). Depending on the procedure and number of ports required, the mother can have from one to several small incisions on her abdomen or a small laparotomy as with the closed procedures. To optimize visual clarity in the uterus when the amniotic fluid is not clear, an amnio-exchange with warmed saline can be used during the procedure to improve visualization of the fetus (Graves et al., 2017). Complications of fetoscopic procedures are bleeding, membrane separation, chorioamnionitis, amniotic fluid leakage, PROM, premature labor, premature birth, and intrauterine fetal demise. PROM and premature labor are the most common complications of MIS and lead to significant fetal morbidity in the form of oligohydramnios, lung hypoplasia, chorioamnionitis, and premature birth (Graves et al., 2017). Additionally, the number of access sites on the maternal abdomen and the size of the fetoscopic instruments have been linked to fetal morbidity with larger diameter instruments significantly decreasing gestation age at birth (Graves et al., 2017). Minimally invasive procedures, as they relate to specific diagnoses, will be discussed elsewhere in the chapter.

Fetal Surgery

Since its introduction in the mid-1960s, fetal therapy, specifically fetal surgery, has evolved to meet the needs of life-threatening fetal diagnoses with continued focus on decreasing the risk to the mother for said procedures. In addition to its primary applications (urinary obstruction and fetal anemia), diagnoses amenable to fetal interventions include MMC, TTTS, cervical neck masses, lung lesions, sacrococcygeal teratoma (SCT), and CDH (Wenstrom & Carr, 2014). As fetal surgical techniques have been validated with randomized controlled trials (RCTs) and now have evidence-based rationales, several aspects of the process require further study, identifying the optimal maternal–fetal dyad, optimal timing for the fetal intervention, and prevention of premature labor and global membrane separation following the procedure (Wenstrom & Carr, 2014). Through rigorous science, scientists and fetal surgeons have identified fetal diagnoses amenable to fetal intervention, extensively studied the natural history of each of the diagnoses, tested potential fetal interventions in animal models prior to humans, and safely carried out such interventions in humans on the fetus, itself, now recognized as a patient (Graves et al., 2017; Upadhyaya & Lander, 2013). Additional work utilizing a minimally invasive approach, developed by modeling laparoscopic surgical approaches and instruments, has further decreased fetal morbidity and mortality as well as decreased maternal risk (Graves et al., 2017). Table 24.2 highlights the milestones in both open and minimally invasive fetal procedures.

Open Fetal Surgery

OFS has long been reserved for the most severe cases in which the life of the fetus is in peril with one exception; the fetus with MMC. The procedure itself is similar to the EXIT procedure described next. The mother is anesthetized with general endotracheal anesthesia in addition to epidural anesthesia. In the case of OFS, the epidural serves two functions, both intraoperative and postoperative pain management for the mother (Moldenhauer & Adzick, 2017). Depending on the fetal position and more importantly the placental position, the hysterotomy will either be anterior or posterior (after the uterus is exteriorized). Regardless of the location of the hysterotomy, it will be performed in the fundus (Moldenhauer & Adzick, 2017). The hysterotomy begins with electrocautery followed by the uterine stapling device to ensure a bloodless operative field and control of the membranes (Harrison & Adzick, 1993; Moldenhauer & Adzick, 2017). The uterus is irrigated continuously

TABLE 24.2

FETAL CONDITIONS AMENABLE TO IN-UTERO TREATMENT

Condition	Intervention
Fetal Therapy: Medical Treatment	
Rh sensitization (anemia)	Red cell transfusion (into umbilical vein)
Pulmonary immaturity	Betamethasone (transplacental)
Vitamin B_{12} deficiency	Vitamin B_{12} (transplacental)
Carboxylase deficiency	Biotin (transplacental)
Supraventricular tachycardia	Digoxin, flecainide, or similar drug (transplacental)
Heart block	Betamimetics (transplacental)
Hypothyroidism	Thyroxine (transplacental)
Adrenal hyperplasia	Steroids
Intrauterine growth restriction	Protein calories (transamniotic)
Severe combined immunodeficiency syndrome	Stem cell transplantation into umbilical vessel
Congenital cystic adenomatoid malformation	Maternal steroid administration
Sickle cell disease	Gene therapy
Fetal Therapy: Surgical Treatment	
Urinary tract obstructions	Closed procedure (i.e., percutaneous catheter placement or fetal bladder cystoscopy)
Twin reversed arterial perfusion	Closed procedure (interruption of blood flow to the abnormal fetus by ablating blood vessels)
Twin-to-twin transfusion syndrome	Closed procedure (laser ablation of intertwin vascular connections)
Diaphragmatic hernia	Closed procedure (i.e., temporary tracheal occlusion with a balloon)
Myelomeningocele	Open procedure (i.e., open repair of spinal defect)
Sacrococcygeal teratoma	Closed procedure (i.e., interruption of blood flow to the tumor by ablating/sclerosing vessels) or open procedure (i.e., resection or debulking of tumor)
Pleural effusion	Closed procedure (i.e., placement of thoracoamniotic catheter for decompression)
Aortic stenosis (hypoplastic left heart syndrome)	Closed procedure (i.e., balloon valvuloplasty)
Hypoplastic left heart syndrome with intact atrial septum	Closed procedure (i.e., balloon septostomy)
Pulmonary atresia	Closed procedure (i.e., balloon valvuloplasty)
Congenital high airway obstruction syndrome	Closed procedure (laser ablation of obstruction) and/or open procedure (delivery via *ex-utero* intrapartum treatment procedure after establishment of fetal airway while on placental bypass)

with warmed lactated Ringer's (LR) or warmed normal saline solution (NSS) to maintain fetal buoyancy, fetal thermoregulation, and uterine distension (Moldenhauer & Adzick, 2017). Although receiving maternal anesthesia via the placenta, the fetus is given additional sedation and a neuromuscular blockade drug (NMBD) for paralysis, as NMBDs do not cross the placenta (Bouchard et al., 2002; H. L. Hedrick et al., 2005; Hirose et al., 2004; Laje et al., 2012). **Quality and Safety: Atropine is administered to the fetus to prevent fetal bradycardia** (Bouchard et al., 2002; H. L. Hedrick et al., 2005; Hirose et al., 2004; Khalek & Johnson, 2013; Laje et al., 2012). The fetus is monitored during the procedure via pulse oximetry and sterile fetal echocardiography as maternal general anesthesia acts as a fetal myocardial depressant (Khalek & Johnson, 2013; Moldenhauer & Adzick, 2017). Additionally, intravenous access is obtained in the fetus for medication and volume administration. For example, premedicating with volume is required for fetal lung lesion resection as removal of a large lesion from the fetal chest can precipitate a rapid decline in fetal cardiac output (Khalek & Johnson, 2013). Once the fetal surgery is complete, and regardless of the defect, the uterus is closed in two layers to make the closure watertight and the LR or NSS is infused until the final suture is placed to return the amniotic fluid levels to normal and allow for intra-amniotic antibiotic to be infused; the infusion catheter is then removed and an omental flap is placed over the sutured hysterotomy to help further seal it (Khalek & Johnson, 2013; Moldenhauer & Adzick, 2017). The laparotomy is then closed, the mother is recovered, and her care then follows a postoperative protocol (Nassr, Erfani, et al., 2017; Peranteau et al., 2014). As with the EXIT procedure, delivery of the pregnancy affected by OFS and all subsequent pregnancies should avoid active labor and be delivered by cesarean delivery to prevent uterine rupture (Graves et al., 2017; Moldenhauer, 2013; Nassr, Erfani, et al., 2017). The timing of a pregnancy subsequent to OFS should be at least 2 years (Nassr, Erfani, et al., 2017).

EXIT Procedure

Ex-utero intrapartum therapy (or treatment), also referred to as an EXIT procedure, is the process of performing a lifesaving intervention on the fetus via an open uterine incision while the mother is deeply anesthetized; the uterus is relaxed and distended and the fetus is partially delivered but remains on placental bypass (Mychaliska et al., 1997). The purpose of the EXIT procedure is to stabilize the fetus prior to birth when there is an anatomic defect that will significantly increase the chance of morbidity and mortality and interfere with the fetus' successful transition to extrauterine life. Initially developed for the establishment and securement of an airway in a fetus that had a prior in-utero tracheal occlusion for CDH, the EXIT procedure can and has been used for the following congenital anomalies: cervical or oropharyngeal teratoma, mediastinal teratoma, cervical lymphangioma, laryngeal atresia, congenital high airway obstruction syndrome (CHAOS), tracheal web, severe subglottic stenosis, facial tumors, resection of large lung lesions, and cannulation for extracorporeal membrane oxygenation (ECMO; Bouchard et al., 2002; Hirose et al., 2004; Laje et al., 2012; Moldenhauer, 2013; Mychaliska et al., 1997).

While the EXIT procedure results in a cesarean-like birth, there are some important distinctions to differentiate one procedure from the other. Once a prenatal diagnosis is made that has proven amenable to the EXIT procedure, a referral must be made to a tertiary center with an established and highly experienced MFM and fetal/pediatric surgery group. The maternal/fetal dyad must first be assessed for appropriateness for the procedure. The prenatal diagnosis must be confirmed utilizing advanced diagnostic techniques such as high-resolution fetal sonography, ultrafast fetal MRI, and fetal echocardiography (Moldenhauer, 2013). Adjuvant testing may include karyotyping and further genetic testing, where indicated. A comprehensive multidisciplinary team is essential in the diagnosis, planning, and execution of the EXIT procedure and should include high-risk obstetricians and MFMs, fetal/pediatric surgeons, anesthesiologists, radiologists, pediatric cardiologist, neonatologists, nurses of varying specialties, advanced practice nurses, social workers, case managers, and potentially an ECMO team (Bouchard et al., 2002; Hirose et al., 2004; Laje et al., 2012; Moldenhauer, 2013). A substantial amount of teaching is required by the multidisciplinary team to help the family understand not only the diagnosis but also the procedure itself including all risks and potential outcomes. **Emergency Alert: Diverging from any of the aforementioned practice recommendations may lead to suboptimal outcomes or even death for both the mother and the fetus.**

The procedure itself involves a very large multidisciplinary team in the operating room that must operate in seamless coordination with each other, especially considering the time constraint, the significance of the procedure, and the size of the patient and corresponding surgical field. Prior to the procedure, the placenta must be mapped and its margins clearly delineated. If the placenta is anterior, options for hysterotomy include classic cesarean incision, fundal incision, or even posterior uterine incision (Bouchard et al., 2002; H. L. Hedrick et al., 2005; Hirose et al., 2004; Laje et al., 2012; Moldenhauer, 2013; Noah et al., 2002). Placental mapping can be difficult in the setting of polyhydramnios that often accompanies airway obstruction (Bouchard et al., 2002; H. L. Hedrick et al., 2005; Mychaliska et al., 1997). In such cases, an amnioreduction can be performed. To start, the mother is positioned supine and slightly in left-lateral decubitus. This facilitates offloading the gravid uterus from the inferior vena cava, which in turn will promote hemodynamic stability in the mother throughout the case (Bouchard et al., 2002; Hirose et al., 2004; Moldenhauer, 2013). The mother is endotracheally intubated and placed under deep general anesthesia to promote uterine relaxation. This is accomplished with inhaled halogenated anesthesia and adjuvant tocolytics, as needed (Bouchard et al., 2002; Hirose et al., 2004; Laje et al., 2012; Moldenhauer, 2013; Mychaliska et al., 1997). Maternal monitoring is standard for a patient under general anesthesia. After abdominal incision, the placenta is again mapped to confirm its position in the uterus and the fetus' position is confirmed with sterile ultrasonography. At this point, an amnioreduction can be performed. The uterus is entered with the use of a specifically designed uterine stapler that discharges absorbable staples and creates a hemostatic, bloodless incision as well as controls the membranes (Harrison & Adzick, 1993). The uterus is continually observed and palpated for contractions. If contractions are detected, additional tocolytics are utilized (Hirose et al., 2004; Moldenhauer, 2013). Through the hysterotomy, the fetus is partially delivered, typically head and neck or head and chest, depending on the location of the defect, diagnosis, or indication for the procedure. To replace lost amniotic fluid, a continuous infusion of warmed NSS or warmed LR solution is infused into the uterus (Bouchard et al., 2002; H. L. Hedrick et al., 2005; Hirose et al., 2004; Laje et al., 2012; Moldenhauer, 2013). This continuous infusion serves several purposes. First, the fetus is kept warm and buoyant and, most importantly, the uterus remains distended and staves off contractions and placental separation. The fetus is continually monitored during the procedure with pulse oximetry and sterile fetal echocardiography and given additional analgesia, although likely sedated via maternal anesthesia, and also given neuromuscular blockade as these

drugs do not cross the placental barrier (Bouchard et al., 2002; H. L. Hedrick et al., 2005; Hirose et al., 2004; Laje et al., 2012). Establishment of the fetal airway is paramount and performed first in all cases due to potential complications and potential need to emergently abort the procedure. Exogenous surfactant is administered when indicated for appropriate preterm gestational age. Peripheral intravenous access is established in the fetus first and later umbilical venous and arterial catheters can be placed, as timing allows. During an EXIT procedure, the fetal surgeon can perform a variety of procedures including laryngoscopy, bronchoscopy (rigid and flexible), orotracheal intubation, tracheostomy, resection of masses or lung lesions, and ECMO cannulation (Hirose et al., 2004; Moldenhauer, 2013). In certain cases, a tracheotomy can be performed followed by orotracheal intubation over a sterile feeding tube or guidewire introduced in a retrograde manner (Bouchard et al., 2002; Laje et al., 2012). Once the indicated intervention is completed and barring any complications, the umbilical cord is clamped, the cord is cut, and the fetus is delivered and given to the awaiting specialized neonatal team for further resuscitation. If additional surgical procedures are necessary, they can be performed once the infant is stabilized. An infant undergoing an EXIT procedure is not assigned Apgar scores, as they are sedated and pharmacologically paralyzed prior to delivery. In ideal conditions, a fetus can remain on placental bypass without complications for approximately 60 minutes, although a procedure time of 150 minutes has been described in the literature (H. L. Hedrick et al., 2005; Hirose et al., 2004; Moldenhauer, 2013). After the fetus is delivered, the hysterotomy and maternal abdomen are both closed and the mother is awoken from anesthesia. Post-EXIT care of the mother is similar to that of a cesarean delivery (Moldenhauer, 2013).

Maternal outcomes following an EXIT procedure are similar to those of women following standard cesarean delivery with regard to blood loss, need for blood product transfusion (low), recovery time, infection rate, and hospitalization (H. L. Hedrick et al., 2005; Hirose et al., 2004; Moldenhauer, 2013; Noah et al., 2002). After an EXIT procedure, secondary to the inherently required large hysterotomy (H. L. Hedrick et al., 2005), active labor must be avoided in subsequent pregnancies and future deliveries should occur via scheduled cesarean delivery. Future fertility is not adversely affected (Hirose et al., 2004; Moldenhauer, 2013).

Anesthesia and Analgesia for Fetal Procedures/Surgery

When anesthesia is administered for fetal surgery or fetal procedures, it is important to remember that two (or more, in the case of multiparity) patients are simultaneously being anesthetized. The risks of anesthesia during pregnancy are multifocal as they relate to the physiologic changes of the mother, which, in turn, cause alterations in pharmacokinetics and pharmacodynamics, and possible adverse effects on the fetus (Box 24.2). Therefore, anesthetizing a pregnant woman during major surgery requires specially trained anesthesiologists who can provide the necessary level of anesthesia and pain management for the maternal–fetal dyad while ensuring the mother's safety and minimal side effects for both patients. Meticulous attention must be paid to perioperative fluids, administration of inhaled halogenated anesthetic gases, the titration of vasopressors and inotropic agents, and accurate assessment of pulmonary vascular permeability as maternal fluid volume overload and pulmonary edema can occur rapidly (Duron et al., 2014; Saracoglu et al., 2016; Saracoglu, Saracoglu, Alatas, & Kafali, 2015). The following must be taken into consideration by the anesthesiologist when anesthetizing the maternal–fetal dyad:

- Decreased peripheral vascular resistance (cardiac output increases with no increase in blood pressure, resulting in a decrease in peripheral vascular resistance)
- Decreased functional residual capacity and an increase in alveolar ventilation (which speeds up induction with inhalation anesthetics)
- Increased oxygen consumption (decreased functional residual capacity combined with increased oxygen consumption predisposes pregnant women to hypoxia)
- Hypotension as a result of aortocaval compression (lying supine, a pregnant woman in the second and third trimesters experiences reduced blood flow back to the heart because of aortocaval compression by the gravid uterus)

The compression of the major abdominal vessels by the gravid uterus when the mother lies supine not only causes maternal hypotension but also causes uterine hypoperfusion. It is for this reason the mother must be tilted slightly on the operating table to ensure the absence of aortocaval compression.

Pregnant women are also more sensitive to inhaled anesthetics because of elevated endorphin levels, and therefore require less inhaled gas (Duron et al., 2014; Saracoglu et al., 2015). Regional anesthetics also require adjustment. The increase in intra-abdominal pressure and venous shunting of blood in the mother enlarges the epidural veins, which decreases the epidural space and decreases the analgesic requirement (Saracoglu et al., 2015).

Maintaining the stability of the fetal cardiovascular system is the most important step in anesthesia management during fetal surgery (Liu et al., 2013). If fetal bradycardia is detected by the surgeons, the surgeon responds by repositioning the fetus to relieve cord compression and the anesthesiologist must respond immediately by raising the maternal blood pressure, increasing maternal oxygenation, and administering tocolytics (Hoagland & Chatterjee, 2017). There are threats to this stability from maternal

Box 24.2

MATERNAL PHYSIOLOGIC CHANGES DURING PREGNANCY AFFECTING ANESTHESIA ADMINISTRATION

- Increased cardiac output (50%–100%)
- Increased plasma volume (40%–55%)
- Increased RBC volume (20%–30%)
- *Relative* anemia and hypoalbuminemia (plasma volume increase > RBC volume increase)
- Decreased serum oncotic pressure
- Decreased blood pressure
- Decreased peripheral vascular resistance
- Increased oxygen consumption
- Altered coagulation; tendency toward hypercoagulopathy
- Increased susceptibility to thromboembolic events
- Increased endorphin and progesterone
- Decreased functional residual capacity
- Increased susceptibility to hypoxia
- Increased pulmonary vascular permeability
- Increased gastric acid secretion
- Decreased LES tone
- Displacement of the pylorus, stomach, LES, and diaphragm
- Increased risk of aspiration during intubation and resultant aspiration pneumonia

LES, lower esophageal sphincter; RBC, red blood cell.

anesthesia and fetal blood loss. Maternal inhalation anesthesia has a direct inhibitory effect on the fetal myocardium depressing its function as well as vasodilation (Liu et al., 2013). This negative effect is only exaggerated the longer the fetus is exposed to inhaled agents. Another threat to the fetal cardiovascular stability is fetal blood loss. Due to the small circulating fetal blood volume (100–110 mL/kg), even the smallest amount of blood loss can lead to hypovolemia, resulting in profound fetal hypotension (Hoagland & Chatterjee, 2017; Liu et al., 2013). Due to the immaturity and the lack of sensitivity of fetal regulatory mechanisms, the fetus is unable to adequately increase its heart rate, cardiac output, and blood pressure to accommodate these stressors. This is what makes fetal acidosis, hypotension, and bradycardia such common and significant threats to fetal well-being during fetal procedures. Fetal oxygenation depends on the maternal arterial oxygen content. If the mother's partial pressure of arterial oxygen, partial pressure of arterial carbon dioxide, and uterine blood flow are maintained within normal limits, fetal anoxia is least likely to occur. Fetal acidosis can occur quickly and it is vital to avoid when at all possible (Saracoglu et al., 2015). Other causes of fetal anoxia are maternal hypotension, which causes a decrease in uterine blood flow, as well as uterine vasoconstriction caused by anxiety, insufficient anesthesia, or vasoactive drugs.

Maternal anesthesia and analgesia for open fetal procedures includes regional anesthesia (epidural or spinal) and deep endotracheal general anesthesia. Regional anesthesia augments general anesthesia intraoperatively and serves as analgesia postoperatively. Deep general anesthesia is important to maintain uterine relaxation throughout the procedure.

Fetal analgesia during fetal procedures or fetal surgery, whether open or MIS, is a multimodal approach. During open procedures, the fetus receives maternal anesthesia via placental transfer. Additional analgesia is given to the fetus despite this transfer to guarantee a pain-free procedure for the fetus. Neuromuscular blockade must be administered directly to the fetus as these drugs do not cross the placental barrier. Typically, a combination of atropine (to prevent fetal bradycardia), fentanyl (half-life of >12 hours in the fetus), and neuromuscular blockade to decrease fetal movement during the procedure is utilized (Nassr, Erfani, et al., 2017). In the setting of fetal bradycardia, additional medications, crystalloid fluids, or blood products can be administered intravenously to the fetus to maintain or regain hemodynamic stability. For minimally invasive procedures, the fetus does not receive anesthesia or analgesia from maternal local or regional drugs. In these cases, the aforementioned combination of medications is administered intramuscularly directly to the fetus. Depending on the procedure performed, the complexity of the procedure, and the instruments required to accomplish said procedure, immobility of the fetus is not always required (Graves et al., 2017). It should be noted that minimally invasive procedures performed on noninnervated fetal tissues (the placenta and umbilical cord) do not require fetal anesthesia or analgesia (Graves et al., 2017; Hoagland & Chatterjee, 2017).

Perioperative and Postoperative Care

Perioperative management of the mother includes the use of tocolytics (magnesium sulfate infusion, indomethacin, and nifedipine). Given the fluid shifts that occur during and after fetal surgery, patients are encouraged to orally hydrate the night before the procedure so that fluids can be restricted intraoperatively and postoperatively. This reduces the risk of pulmonary edema in the immediate postoperative period (Moldenhauer & Adzick, 2017).

After the procedure, the mother remains in the hospital for approximately 4 days. During that time, daily ultrasounds and echocardiography are performed to assess fetal well-being and the quiescence of the uterus. The current tocolytic regime begins with indomethacin to the mother before surgery and over the next several days. Indomethacin is the drug of choice because it inhibits the synthesis of prostaglandins released during uterine manipulation. The mother is discharged on activity restrictions (like modified bed rest), oral nifedipine, and extensive teaching on signs and symptoms of preterm labor. She will come back once or twice weekly for fetal evaluation (i.e., nonstress test [NST]) and ultrasound (i.e., amniotic fluid index). If rupture of membranes, chorioamniotic separation, or preterm labor occur, the mother will be rehospitalized, placed on bed rest, and continuously monitored.

Diagnoses

Congenital Anomalies

Cardiac. Indications for fetal cardiac intervention include critical aortic stenosis, hypoplastic left heart syndrome (HLHS) with intact atrial septum, and pulmonary atresia with intact ventricular septum (Nassr, Erfani, et al., 2017). Critical aortic stenosis presents during the second trimester and is identified by echocardiography. The echocardiography will reveal left ventricle dilation with progressive dysfunction; this evolves into HLHS. The goal of fetal intervention is to prevent progressive left ventricular dysfunction and ultimately HLHS. Under continuous ultrasound guidance, a needle is aligned with the left ventricular outflow tract, the trocar is removed, and a guide wire with a preloaded balloon is advanced through the aortic valve. Once the wire is in the correct position, the balloon is inflated, and the valve is dilated. The balloon is then deflated and removed (Nassr, Erfani, et al., 2017).

Fetuses with HLHS with intact atrial septum will be hypoxemic at birth due to increased left atrial pressures resulting in lung disease (Rintoul et al., 2018). They will have severe metabolic and respiratory acidosis resulting in a high mortality rate. Fetal treatment for HLHS with intact atrial septum involves an atrial septostomy with or without stent placement. Pulmonary atresia with intact ventricular septum results in right ventricle hypoplasia. The goal of fetal intervention is to restore biventricular circulation by performing a pulmonary valvuloplasty (Rintoul et al., 2018).

Congenital Cystic Adenomatoid Malformations. Congenital cystic adenomatoid malformations (CCAM) is a developmental abnormality of the fetal lung parenchyma that occurs in every 1:15,000 to 1:25,000 live births (Derderian et al., 2015; Euser et al., 2016). In normal pulmonary development, the HOXB-5 gene is present during the pseudoglandular phase and then decreases over time, specifically during the canalicular phase. PDGF-B becomes predominant in the canalicular phase and decreases in the saccular phase. As these lung lesions grow, they can be large enough to obstruct the esophagus, which leads to polyhydramnios and increases the risk of preterm labor and birth (Khalek & Johnson, 2013). The lesion can also cause significant mediastinal shift resulting in pulmonary hypoplasia, impaired venous return, cardiac failure, and hydrops (Khalek & Johnson, 2013).

There are several classification systems utilized to describe these lung lesions, with the modified Stocker classification being the most common (Pogoriler, Swarr, Kreiger, Adzick, & Peranteau, 2017). Although there are five classifications that fall under the modified Stocker, types I and II are the most common. Type I refers to large cysts (macrocystic) and type II refers to small cysts (microcystic). Macrocystic lesions are described as lung lesions with one or more cysts greater than 5 mm. These lesions often grow throughout pregnancy and are amenable to aspiration and thoracoamniotic shunt (TAS) placement (Derderian et al., 2015; Peranteau et al., 2016). TAS placement can decrease the CCAM volume by 50% to 80%, ultimately reducing the intrathoracic mass effect (Khalek &

Johnson, 2013; Peranteau et al., 2015). Postshunt placement complications include premature rupture of membranes, preterm labor, chorioamniotic membrane separation, and infection (Khalek & Johnson, 2013). Chest wall deformities are a known risk when a TAS is placed early in gestation (18–20 weeks) and should be discussed during the fetal consult. In addition, there is a risk of shunt occlusion, malfunction, or dislodgement (Peranteau et al., 2015). Microcystic lesions, cysts that are less than 5 mm, generally plateau or decrease in size after 26 to 28 weeks' gestation and are amenable to prenatal betamethasone administration (Derderian et al., 2015; Macardle et al., 2015).

Antenatal betamethasone has become the standard of care for fetuses with a microcystic or mixed lesion whose CCAM volume ratio (CVR) is 1.6 or more (Derderian et al., 2015; Khalek & Johnson, 2013; Peranteau et al., 2016). The CVR is calculated by multiplying the CCAM length, width, height, and a constant of .52 and dividing it by the head circumference (Euser et al., 2016).

$$\frac{\text{Length (cm)} \times \text{height (cm)} \times \text{width (cm)} \times .52}{\text{Head circumference}}$$

Studies have shown that CVR of 1.6 or more increases the risk of the fetus developing hydrops. Although the mechanism of action for antenatal steroids is unknown, it is hypothesized that betamethasone downregulates several genes that are related to abnormal lung development. For fetuses with CCAM, HOXB-5 and PDGF-B remain persistently elevated and it is theorized that steroids stop these elevations and impede CCAM growth (Derderian et al., 2015).

For those symptomatic lesions that are unresponsive to steroids, OFS may be performed. If significant mediastinal shift is present, recommendations include EXIT procedure with lobectomy while on placental bypass or elective cesarean delivery and immediate lobectomy after birth (Khalek & Johnson, 2013). If the fetus is asymptomatic, postnatal resection of the lesion is recommended given the risk of lobe infections or malignancy (Pogoriler et al., 2017). Histology reports have included cases of myxosarcoma, embryonal rhabdomyosarcoma, pleuropulmonary blastoma, and bronchoalveolar carcinomas (Khalek & Johnson, 2013). Once a lobectomy has been performed, the remaining normal ipsilateral lung continues to grow to fill the chest and there are no residual respiratory problems (Khalek & Johnson, 2013).

Congenital Airway Malformations and Neck Masses. CHAOS is a complete or near-complete airway obstruction typically caused by laryngeal or tracheal atresia, but in rare cases can be caused by isolated tracheal stenosis, mucosal web, severe micro- or retrognathia, subglottic stenosis, or extrinsic compression by a large cervical mass (e.g., teratoma or lymphangioma; M. H. Hedrick et al., 1994; Lim et al., 2003). CHAOS is uniformly fatal if not treated with a fetal intervention (including EXIT procedure). To date, no fetus has survived CHAOS without fetal intervention (Ryan, Somme, & Crombleholme, 2016). Regardless of the etiology, the pathophysiology of fetal upper airway obstruction is such that it prevents egress of the fluid produced in the lungs to the amniotic space. This fluid is usually produced under a pressure that favors movement out through the fetal mouth and is partly aided by fetal breathing movements. Sonographic findings of CHAOS include a bilaterally flattened or everted diaphragm, large, overdistended (fluid-filled), echogenic lungs that compress the mediastinum, dilated large airways distal to the obstruction, and fetal ascites or hydrops that result from compression of the heart and great vessels (M. H. Hedrick et al., 1994). If hydrops does not develop in utero, a fetus with CHAOS may be delivered via the EXIT procedure, which maintains the baby on placental support until an airway is established via orotracheal intubation or tracheostomy (Mychaliska et al., 1997). Approximately one-third of fetuses with CHAOS will spontaneously perforate the atresia into the larynx or the esophagus, allowing for egress of lung fluid, reducing the compression on the mediastinum and resolution of fetal hydrops (Rintoul et al., 2018). If the atresia does not spontaneously perforate, in the setting of hydrops, a fetoscopic laser can be used to perforate the laryngeal or tracheal atresia, allowing for resolution of the hydrops prior to the EXIT procedure; laser perforation of the atresia does not negate the need for delivery via EXIT. Use of the EXIT procedure in CHAOS cases can offer an improved prognosis and the potential for excellent long-term outcome of these fetuses that otherwise would not survive.

Extrinsic causes of upper airway obstruction that can present prenatally are epignathus, epulis, mandibular hypoplasia, large cervical teratoma, large lymphatic malformations, thoracic teratomas, and space occupying lung lesions (Ryan et al., 2016). If there is upper airway obstruction, regardless of the etiology, these fetuses should be delivered via the EXIT procedure for the safest transition to extrauterine life and best possible outcomes. During the EXIT procedure, fetal surgeons can perform laryngoscopy, bronchoscopy (rigid and flexible), orotracheal intubation, tracheostomy, and even resection of the obstructing mass. Once the airway is obtained and ventilation is established, the fetus can be delivered and transitioned to the awaiting neonatology team in a controlled manner for proper resuscitation and stabilization.

Congenital Diaphragmatic Hernia. CDH occurs when the diaphragm fails to close and the abdominal contents migrate into the chest through the hernia. CDH occurs in every 1:2,500 live births; left-sided lesions are more common than right-sided, and bilateral lesions are rare (Deprest et al., 2005; Peralta, Jani, Van Schoubroeck, Nicolaides, & Deprest, 2008). Given the herniation of abdominal contents into the chest cavity, the lungs develop with fewer alveoli, thickened alveolar walls, increased interstitial tissue, and diminished alveolar space and gas-exchange surface area (Deprest et al., 2005). Also, the pulmonary vasculature is abnormal. There are fewer vessels per lung volume, medial hyperplasia, and peripheral extension of the muscle layer into the smaller intraacinary arterioles, and adventitial thickening. Based on these two developmental abnormalities of the lung, CDH is associated with high postnatal mortality due to pulmonary hypoplasia and/or pulmonary hypertension (Deprest et al., 2005; McHugh et al., 2010; Peralta et al., 2008). CDH can be associated with chromosomal anomalies, as well as syndromes (Deprest et al., 2005).

The evolution of high-resolution ultrasound and fetal MRI have made the diagnosis of CDH possible prenatally, as well as determining lung-to-head ratio (LHR; Deprest et al., 2005; Victoria, Danzer, & Adzick, 2013). This is calculated by measuring the lung area (length 1 × length 2) and dividing that number by the head circumference. The main limitations of LHR are its dependence on gestational age, the variability in measurements, and compression of contralateral lung from visceral organs (Victoria et al., 2013). Given these limitations, observed compared with expected (O/E) LHR was developed to correct for gestational age. Fetuses with an O/E LHR less than 15% have extreme pulmonary hypoplasia, which is associated with poor survival rate. Infants with an O/E LHR of 15% to 25% have severe pulmonary hypoplasia and a predicted survival rate of 20%. Those with an O/E LHR of 26% to 35% have moderate pulmonary hypoplasia and an expected survival rate of 30% to 60%. Lastly, fetuses with an O/E LHR between 36% and 45% will have mild pulmonary hypoplasia and have a survival rate of greater than 75% (Victoria et al., 2013).

Historical fetal intervention included OFS to repair the hernia and tracheal clip to improve lung growth. Both modalities resulted in poor outcomes, especially for those fetuses where the liver is

herniated into the chest. During OFS, reduction of the liver into the abdomen kinks the umbilical vein and leads to fetal death (Deprest et al., 2005). Most recently, fetal research has been focused on fetoscopic endoluminal tracheal occlusion (FETO) that prevents egress of lung fluid, which increases lung tissue stretch and triggers lung growth, reversing the development of pulmonary hypoplasia (Deprest et al., 2005; Peralta et al., 2008). The timing of FETO is important, in addition to the duration of occlusion, as the goal is to balance alveolar type I and II cells, surfactant synthesis, and total alveolar phospholipid content. The balloon is placed between 26 and 28 weeks' gestation and removed around 34 weeks' gestation, allowing for vaginal delivery or referral back to a hospital closer to home (Figure 24.1). An important complication of FETO is rupture of membranes and the risk for preterm delivery. If the balloon is in place or is unable to be deflated prior to delivery, an EXIT procedure should be performed. In the case where a delivery is imminent and an EXIT procedure cannot be executed, surgery staff specialty trained in balloon retrieval must be present at the delivery for immediate retrieval via bronchoscopy prior to resuscitation.

With the advancements in obstetrics and neonatology, interventions like prenatal corticosteroid administration, high-frequency oscillatory ventilation (HFOV), surfactant administration, inhaled nitric oxide (iNO), and ECMO have positively impacted the postnatal survival of newborns with CDH (Deprest et al., 2005; McHugh et al., 2010).

Myelomeningocele. Routine maternal serum alpha-fetoprotein (MSAFP) screening that is outside the normal range alerts healthcare providers to directly sonograph the fetal spine. The ultrasonographer will also evaluate the head for frontal bone scalloping (lemon sign), for abnormality of the cerebellum (banana sign), for Arnold-Chiari II malformation (hindbrain herniation), and for hydrocephaly. Neural tube defects can occur either as a flat defect without a fluid-filled sac covering (myeloschisis), with a membranous covering (meningocele), or membranous covering with extrusion of the spinal cord into the fluid-filled sac (MMC). MMC is the most common congenital central nervous system anomaly that occurs in 3.4:10,000 live births (Adzick et al., 2011; Farmer et al., 2018). MMC occurs when the neural tube fails to close during the fourth week of gestation. It is characterized by a fluid-filled sac that contains the spinal cord and nerves (Moldenhauer & Adzick, 2017). This results in hydrocephaly, hindbrain herniation, and damaged nerves that lead to long-term morbidity and mortality (Moldenhauer & Adzick, 2017). Survivors have paralysis, bowel dysfunction, and bladder dysfunction, and the majority have Arnold-Chiari II malformation. This malformation includes hindbrain herniation, brainstem abnormalities, low-lying venous sinuses, and a small posterior fossa (Adzick et al., 2011). Given this constellation, hydrocephalus and developmental brain abnormalities have been well documented, in addition to the effects on motor, cranial nerve, and cognitive functions (Adzick et al., 2011).

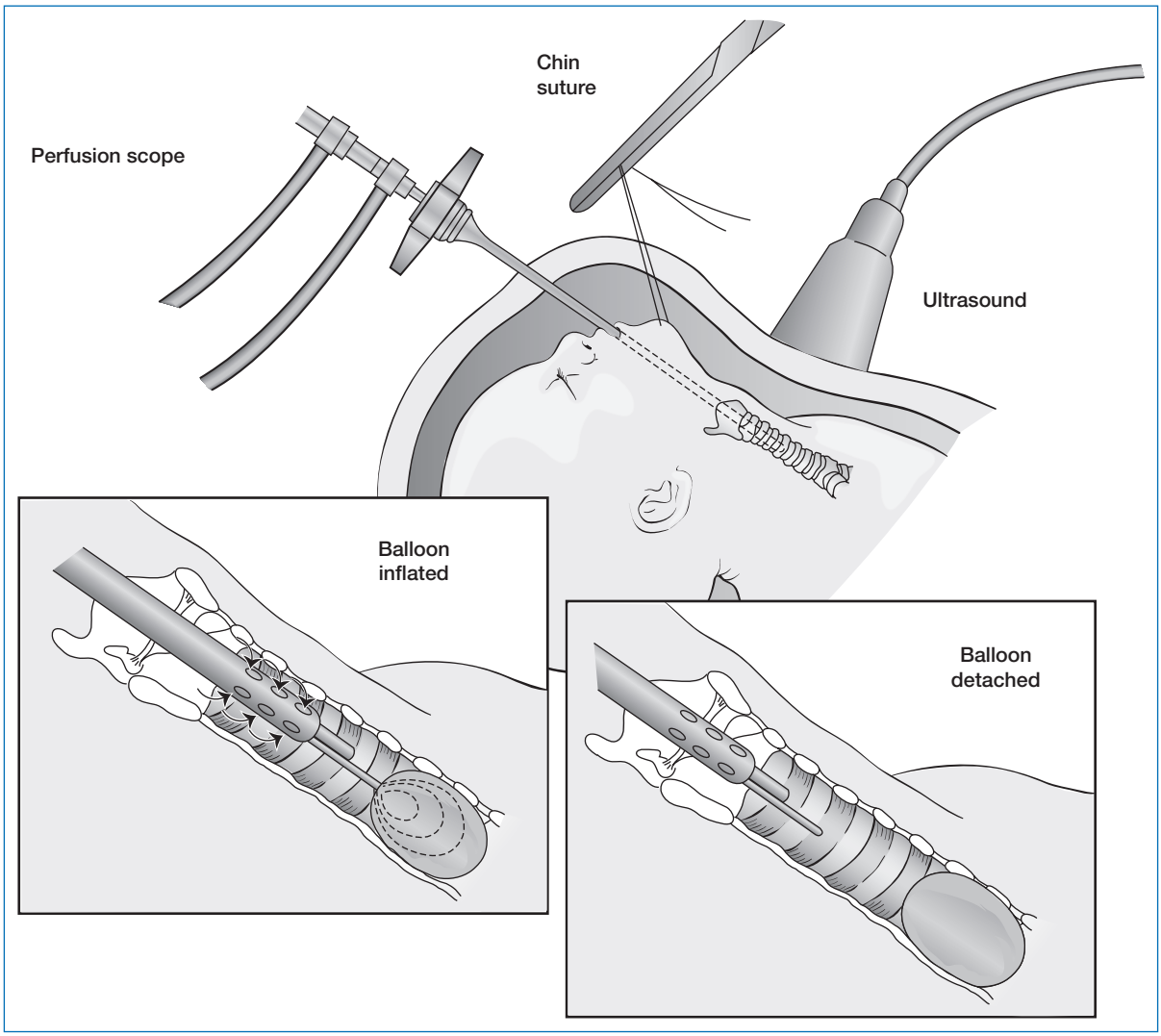

FIGURE 24.1 Fetal tracheal occlusion with balloon.

Initial attempts at in-utero MMC closure were performed endoscopically by covering the neural placode with a split-thickness skin graft (Moldenhauer & Adzick, 2017). Given that the outcomes were poor, OFS techniques were then explored. In 2003, the Management of Myelomeningocele Study (MOMS) trial was started and sponsored by the National Institutes of Health. This trial was a prospective, multicenter randomized trial that compared prenatal and postnatal MMC closure. There were strict inclusion and exclusion criteria to ensure the safety of both the mother and the fetus (Adzick et al., 2011).

The MOMS trial found that children in the prenatal surgery group were more likely to walk independently due to improved motor function, had decreased need for ventriculoperitoneal (VP) shunt placement when fetal repair occurred between 20 and 24 weeks' gestation, and improved psychomotor and mental development (Farmer et al., 2018; Moldenhauer & Adzick, 2017; Tulipan et al., 2015). Although prenatal surgery does not seem to impact the need for clean intermittent catheterization, it has significantly impacted bladder trabeculation, vesicoureteral reflux, and open bladder neck (Moldenhauer & Adzick, 2017).

Maternal–fetal complications of prenatal MMC closure include chorioamniotic membrane separation, spontaneous membrane rupture, oligohydramnios, and spontaneous labor. Like other fetal therapies and interventions, there is an increased incidence of maternal pulmonary edema, uterine dehiscence, and need for blood transfusion at the time of delivery (Moldenhauer & Adzick, 2017; Tulipan et al., 2015). Preterm delivery, with an average gestational age of 34 weeks, and central apnea, regardless of gestational age, were identified in the neonatal period (Moldenhauer & Adzick, 2017).

Obstructive Uropathy. Fetal LUTO is a serious condition in the fetus with significant risk for morbidity and mortality in the neonatal period if left untreated (Haeri, 2015). Hallmark presentation on ultrasound is a dilated bladder with a thickened wall and bilateral hydroureteronephrosis (Graves et al., 2017; Haeri, 2015). The severe forms of the condition lead to a distended/dilated urinary system with resultant renal dysplasia and oligohydramnios that results in pulmonary hypoplasia and deformation of the facies and distal extremities. The incidence of significant LUTO is 1 in 500 pregnancies, but is likely underestimated, with 10% of cases associated with trisomies 13, 18, or 21 (Haeri, 2015; Wu & Johnson, 2009). There is a strong male predominance (Clayton & Brock, 2014; Wu & Johnson, 2009). The etiology for LUTO is typically PUVs or urethral atresia. The natural history of obstructive uropathy is variable and depends on fetal gender, severity, and gestational age at onset of the obstruction (Wu & Johnson, 2009). Outcomes of the diagnosis and subsequent treatment of LUTO rely on two major factors: degree of pulmonary hypoplasia and degree of renal disease (Wu & Johnson, 2009). When suspected, fetal urinary anatomy is followed closely with ultrasound for evidence of dilatation and the amniotic fluid volume must also be closely monitored for oligohydramnios. When anomalous signs are present, vigilant prenatal testing should ensue to determine candidacy for fetal intervention. Genetics should be thoroughly evaluated as should fetal urine samples for electrolyte concentrations and renal morphology. Fetal urine samples are obtained by needle aspiration under ultrasound guidance. Two or three samples should be obtained 24 to 48 hours apart as the initial sample(s) contain stagnant urine that can skew chemistry results (Haeri, 2015). If the severity of the individual fetal obstruction is suitable for fetal intervention and the family consents, fetal intervention is planned. The three options for fetal intervention are vesicoamniotic shunt (most common), valve ablation, and fetal vesicostomy (Haeri, 2015).

Vesicoamniotic shunting (VAS) is a closed, minimally invasive fetal procedure performed with ultrasound guidance under local maternal analgesia. Due to oligohydramnios, an amnioinfusion is required prior to the start of the procedure (Haeri, 2015). Fetal analgesia and neuromuscular blockade are administered either IV via the umbilical vein or IM in the fetal deltoid. A double pigtail catheter is deployed via needle with the distal end in the fetal bladder and the proximal end in the amniotic space. This allows the fetal bladder to drain, decreases dilation of the urinary system, staves off renal dysplasia, and resolves oligohydramnios. Shunt displacement is a common complication of this procedure and occurs in more than 40% of clinical cases, sometimes necessitating a repeat procedure (Wu & Johnson, 2009).

Fetal cystoscopy is an experimental treatment that can both diagnose the cause of the obstruction and relieve it (in the case of PUV). Fetal cystoscopy is a fetoscopic procedure performed in conjunction with ultrasound guidance. Amnioinfusion is not required with this procedure, but more regional maternal analgesia is required (Haeri, 2015). Fetal anesthesia is similar to that used in VAS. For the procedure, a trocar is inserted into the fetal bladder and the fetoscope is advanced through the trocar toward the urethra. If a membrane-like obstruction of the urethral lumen is noted, PUV can be confirmed and the valves can be ablated with laser ablation, hydroablation, or guidewire ablation (Graves et al., 2017). If the obstruction does not appear membrane-like, urethral atresia is confirmed and no attempt to ablate the obstruction is made.

Fetal vesicostomy is accomplished with OFS. This procedure is not regularly performed due to a paucity of data coupled with maternal and perinatal morbidity (Haeri, 2015). Despite the efforts of scientists studying the condition or the surgeons treating it, long-term survival and long-term renal function remain disappointing. In recent studies, 2-year survival rates ranged from 35% to 54% (Graves et al., 2017) and it has been elucidated that prenatal treatment of LUTO does not negate the need for dialysis or renal transplant (Graves et al., 2017; Haeri, 2015; Nassr, Shazly, et al., 2017; Wu & Johnson, 2009).

Sacrococcygeal Teratoma. SCT is the most common germ cell tumor in neonates and children occurring in 1 in 30,000 to 45,000 live births (Yao, Li, Zheng, Dong, & Xiao, 2014). SCT arises from the coccyx and is composed of tissues from all three germ layers (endoderm, mesoderm, and ectoderm; Partridge et al., 2014; Van Mieghem et al., 2014; Yao et al., 2014). SCTs are classified by the Altman classification system, with Altman type I being completely external and Altman type IV completely internal. Altman types II and III have both internal and external components, with type II a little more external and type III a little more internal. Type IV tumors, because they are completely internal, can be missed on prenatal imaging. Also, because they are all internal, type IV SCTs can have considerable mass effect on surrounding structures. The bladder, rectum, and large and small bowel can be displaced or distorted due to the teratoma. This becomes important in the postnatal period, as voiding and stooling can be negatively affected. Even after the internal teratoma is resected, residual effects of the prior displacement can remain. SCTs, regardless of type, are composed of mature or immature tumor elements on pathologic examination and rarely may contain malignant elements (Partridge et al., 2014). Teratomas with mature elements are the least likely to recur and have the lowest potential for malignancy. Immature elements have an increasing risk for both recurrence and malignant transformation. Evidence of yolk sac elements has the highest malignancy potential and these infants are usually treated with chemotherapy in the neonatal intensive care unit (NICU) or early in infancy.

An internal cystic teratoma does not exert the same mass effect on surrounding structures as a solid teratoma would by virtue of the cysts' ability to be compressed. Solid, vascular SCTs, on the other hand, can exhibit significant mass effect when

internal. Solid, vascular SCTs also create a vascular "steal" of blood whether internal or external, which increases the workload of the fetal heart (Van Mieghem et al., 2014; Yao et al., 2014). The fetal heart has to pump blood to the body of the fetus as well as to the low-resistance vascular bed of the SCT, causing high-output cardiac failure in the fetus that can lead to hydrops and, in extreme cases, maternal mirror syndrome and placentomegaly (H. L. Hedrick et al., 2004; Van Mieghem et al., 2014). For example, "normal" fetal combined cardiac output (CCO) is 400 mL/kg/minute. Fetuses with a CCO greater than or equal to 750 mL/kg/minute are at greatest risk for developing hydrops. Polyhydramnios is another common sonographic finding with SCT. Polyhydramnios increases maternal discomfort, creates marked distension of the uterus, and puts the pregnancy at risk for preterm labor and premature delivery. The etiology of polyhydramnios in the setting of SCT is not fully elucidated, but it is believed to be linked to placentomegaly.

OFS has historically been the treatment of choice for pregnancies complicated by SCT and its sequelae, including polyhydramnios, high-output cardiac failure, and hydrops. It is important for best outcomes to intervene on the fetus early in the development of hydrops (Rintoul et al., 2018). Once hydrops is diagnosed, absence of fetal intervention carries a mortality rate of 100% (H. L. Hedrick et al., 2004). The goal of OFS for SCT is to debulk the external component of the teratoma and ligate the large vascular connections, thereby cutting off the tumor's blood supply and ideally reversing the high-output cardiac failure and hydrops (H. L. Hedrick et al., 2004). During OFS, no attempt is made to resect the internal component (if one exists) or to remove the coccyx. Resection of the remaining teratoma and removal of the coccyx happens in the postnatal period when the neonate is stabilized and prepared for surgery. By definition, the teratoma is not definitively resected until the coccyx is removed. Failure to remove the coccyx results in a 30% to 40% risk of recurrence. There are also minimally invasive fetal interventions employed to ameliorate the complications of SCT and to prolong the pregnancy such as amnioreductions and cyst aspiration (H. L. Hedrick et al., 2004). Others include vascular coiling, embolization, sclerotherapy, monopolar cautery, laser ablation, and radiofrequency ablation (Van Mieghem et al., 2014). The latter group of interventions has been associated with thermal injury to the fetus after laser ablation or RFA, extratumoral spread of the embolizing or sclerosing agents, and hemorrhage (Graves et al., 2017; Van Mieghem et al., 2014).

Infants with SCT are followed closely in the postnatal period and in the long term (usually up to 3 years) with laboratory studies (alpha-feto protein levels), careful physical examination and imaging for recurrence, and malignant transformation (H. L. Hedrick et al., 2004; Padilla et al., 2017). Risks for recurrence and malignant transformation are tumor spillage at time of resection, failure to remove the coccyx, yolk sac pathology, and incomplete resection of the tumor (Padilla et al., 2017). Long-term functional sequelae of SCT, whether debulked prenatally or not, are constipation, fecal incontinence, urinary incontinence, neurogenic bladder, vesicourethral reflux, and sexual dysfunction. Partridge et al. (2014) determined that higher risks for long-term functional sequelae increased with higher Altman typing and with prenatal imaging evidence of gastrointestinal or urologic obstruction. A longitudinal study conducted in 2007 found that functional sequelae of SCT improve over time and the adults studied had complications similar to their age-matched controls (Cozzi et al., 2008). Despite the data and complications described here, survival for infants with SCT is rather high with up to 50% of prenatally diagnosed SCTs following uneventful antenatal, perinatal, and postnatal courses (Nassr, Erfani, et al., 2017).

Fetal Conditions

Amniotic Band Syndrome. Amniotic band syndrome is a rare prenatal complication that occurs in 1:1,200 to 1:15,000 live births (Javadian et al., 2013). The cause remains unknown, but it is hypothesized that there is a primary defect or early disruption of the amnion that results in the mesodermal matrix production, resulting in band development (Derderian, Iqbal, Goldstein, Lee, & Hirose, 2014). The syndrome can lead to fetal demise if there is umbilical cord strangulation or a deformity of a limb or even limb amputation (Graves et al., 2017; Javadian et al., 2013). The presentation, severity, and outcome depend on the location of the bands and timing of damage. Utilization of ultrasound to monitor blood flow to the affected limb and/or umbilical cord entrapment is important to determine the timing of fetal intervention. Ultrasound findings include, but are not limited to, distal limb edema, abnormal doppler flow, and visualization of the band (Graves et al., 2017). The fetal intervention includes using fetoscopy for amniotic band release (Graves et al., 2017; Javadian et al., 2013). Derederian et al. (2014) found that after fetoscopic release of the band, there was improved blood flow, in addition to limb preservation and function verified in the postnatal period.

TTTS and Twin Reversed Arterial Perfusion (TRAP). TTTS is the most common severe and most challenging complication of monochorionic twin pregnancies (Crombleholme, 2003). The incidence of TTTS is between 10% and 15% of monochorionic pregnancies and accounts for 17% of mortality in twin gestations despite its low incidence (Rintoul et al., 2018). TTTS is a complication of monochorionic diamniotic twins characterized by vascular anastomoses at the placental level (chorioangiopagus) that results in an imbalance of flow from one twin to another. This unequal sharing of the monochorionic placenta usually can be visualized on ultrasound; insertion of the smaller (or donor) twin's umbilical cord often is marginal or velamentous, whereas the larger (or recipient) twin's cord inserts into the placenta centrally. The aberrant vascular communications result in a net shunting of blood that can be detected by Doppler ultrasonography. The vessels in question are unpaired, resulting in flow from the donor fetus to the recipient fetus. Doppler studies demonstrate the characteristic pulsatile arterial blood flow on the donor's side, whereas a continuous venous flow is noted on the recipient's side. Other sonographic evidence of TTTS is severe oligohydramnios or anhydramnios in the sac of the donor twin (also known as the "stuck twin") and polyhydramnios, pulmonary hypertension, and hypertrophic cardiomyopathy caused by chronic hypervolemia noted in the recipient twin.

Initial criteria for diagnosing TTTS in utero was based on the criterion derived from neonatal standards for twin birth weight discordance and hemoglobin levels. This was later proven unreliable when the validity of this criterion could not be validated when comparing with values for monochorionic twins without evidence of TTTS and samples of dichorionic twins (Crombleholme, 2003). More recently, the severity of the condition may be assessed using the Quintero staging system (Table 24.3). Not only does this staging system mirror the progression of disease, but it has also been shown to be important in establishing the prognosis (Quintero et al., 1999). Laser photocoagulation is offered for stages II to IV and stage I on a case-by-case basis. Typically outcomes for type I when comparing expectant management and photocoagulation are similar (Nassr, Erfani, et al., 2017). If left untreated, TTTS is lethal and carries perinatal mortality rates as high as 80% or 90% (Graves et al., 2017; Wenstrom & Carr, 2014).

Original treatment proposals for TTTS included intertwin membrane microseptostomy designed to restore amniotic fluid volume equality without the need for repeated amnioreduction

procedures. An investigation of this therapy seemed to suggest microseptostomy was more successful than serial amnioreductions as defined by survival. The study was small and uncontrolled, and its results could not be duplicated by a second retrospective single-institution series comparing serial amnioreductions with microseptostomy. The original investigators then performed and reported results from a multicenter, prospective, randomized clinical trial that again compared microceptostomy with amnioreductions and confirmed the former was not superior to the latter when comparing survival rates (Crombleholme, 2003).

De Lia, Cruikshank, and Keye (1990) first described laser photocoagulation of intertwin vessels for the treatment of TTTS. The results reported similar survival rates when compared with the amnioreduction versus microseptostomy study but superior results when comparing neurologic outcomes (De Lia, Kuhlmann, Harstad, & Cruikshank, 1995). Later, selective laser photocoagulation was proposed and attempted. Selective laser photocoagulation differed from the original nonselective photocoagulation in that the selective procedure did not photocoagulate all vessels crossing the intertwin membrane but, rather, only photocoagulated direct arterial-arterial and veno-venous connections as well as any unpaired artery leading to a cotyledon that had a corresponding vein leading to the other twin's umbilical cord (Crombleholme, 2003). In cases of severe TTTS, selective fetoscopic laser photocoagulation of the communicating vessels (see Figure 24.2) has now become the surgical standard of care after a large European study comparing laser photocoagulation with serial amnioreductions was stopped early for efficacy of laser photocoagulation (Graves et al., 2017; Nassr, Erfani, et al., 2017; Senat et al., 2004; Wenstrom & Carr, 2014). Amnioreductions are still performed for maternal comfort and to improve fetal perfusion by reducing the distending pressure at the uteroplacental interface.

Fetoscopic umbilical cord coagulation is a procedure reserved for the most severe TTTS cases when the recipient twin shows sonographic signs of irreparable cardiomyopathy and who is not expected to survive (Crombleholme, 2003). The premise for this approach posits that cord coagulation and sacrifice of the recipient twin will stop progression of the syndrome, allow for delivery later in gestation for the donor twin, and improve the outcomes for the donor twin, particularly neurologically speaking. During this procedure, the cord of the recipient twin is coagulated, but the vascular communications between the donor twin and the placenta within the recipient twin's space are preserved. There are reports of restored fetal growth of the donor twin, normalization of amniotic fluid volumes, and a donor twin that is neurologically intact at time of delivery; albeit premature (Crombleholme, 2003). For these difficult cases, cord coagulation may be the best chance of survival for at least one of the twins. Other methods of selective fetal reduction include ultrasound-guided bipolar cord coagulation and radiofrequency ablation.

Another disorder of monochorionic twin gestation is TRAP sequence. With TRAP, one twin, who is acephalic and acardiac,

TABLE 24.3

QUINTERO STAGING SYSTEM FOR TWIN-TO-TWIN TRANSFUSION SYNDROME

Quintero Staging System	
Stage I	The fetal bladder of the donor twin remains visible sonographically.
Stage II	The bladder of the donor twin is collapsed and not visible by ultrasound.
Stage III	Critically abnormal fetal Doppler studies noted. This may include absent or reversed end-diastolic velocity in the umbilical artery, absent or reverse flow in the ductus venosus, or pulsatile flow in the umbilical vein.
Stage IV	Fetal hydrops present
Stage V	Demise of either twin

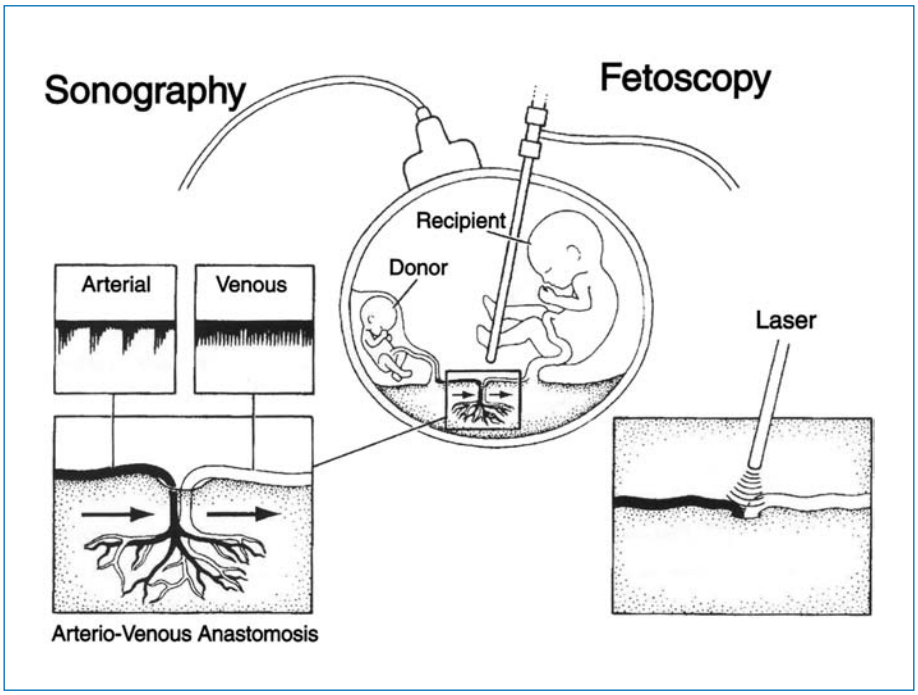

FIGURE 24.2 Fetoscopic laser ablation of the placental intertwin vessels.

is connected to the co-twin in a parasitic fashion. The second twin, or "pump twin," is anatomically normal with normal vascular connections to the placenta. The anomalous twin receives its blood supply from direct vascular connections to the normal twin, which, left untreated, will result in high-output cardiac failure and increased mortality in the "pump" twin. To save the normal twin and increase outcomes and overall survival, blood flow to the anomalous twin must be permanently interrupted. Methods of interrupting flow between the twins affected by TRAP are those outlined earlier for selective fetal reduction.

FETAL THERAPY: NEW HORIZONS

Today, organizations like the North American Fetal Therapy Network (NAFTNet) and the International Fetal Medicine and Surgery Society (IFMSS) support education and research for fetal diagnoses and therapies, in addition to promoting collaboration among fetal therapy centers around the world. IFMSS has an international registry that tracks the number, type, and outcome of fetal surgical attempts.

Further research for fetuses with MMC should be built upon the research studies that showed placenta-derived mesenchymal stem cells significantly improve motor function. Furthermore, transamniotic stem cell therapy and basic fibroblast growth factor sponges have been studied in rodent models for coverage of the MMC defect (Farmer et al., 2018; Moldenhauer & Adzick, 2017). NAFTNet has also sponsored the development of the Fetal Myelomeningocele Consortium and outcomes registry that will provide a way to track outcomes and guide future research (Moldenhauer & Adzick, 2017).

Surgeons at Texas Children's are experimenting with performing minimally invasive fetoscopic procedures by removing almost all of the amniotic fluid and instilling CO_2 into the uterus, thus creating a larger operative space. By doing so, these surgeons posit that larger, more complicated surgeries (such as MMC repair) can be performed, negating the need for OFS that carries higher risk of maternal morbidity (Nassr, Erfani, et al., 2017). It is their hope that this new approach will better anchor the fetal membranes to the uterine wall and prevent premature rupture of membranes and chorioamniotic separation that often comes with fetoscopic repair of MMC (Nassr, Erfani, et al., 2017). Critique of this experimental approach includes the risk of inducing fetal acidosis with the instillation of CO_2 into the uterine environment. Surgeons evaluating the procedure have not found this to be a complication to date, but theorize fetal acidosis can be avoided with maternal hyperventilation. The same group at Texas Children's also theorizes gastroschisis may be another fetal diagnosis that will benefit from fetal intervention. They suggest identifying complicated gastroschisis early and either covering or closing the defect will prevent some or all of the morbidity associated with the diagnosis of gastroschisis (Nassr, Erfani, et al., 2017). A multicenter group from UCSF, the University of California (UC), Berkeley, and Caltech are currently researching the production and use of a biocompatible adhesive that would be used to seal the fetal membranes prior to performing fetal interventions to prevent PROM (Table 24.5). They are modeling their adhesive after the adhesive properties of mussels' attachment to wet rocks (Graves et al., 2017).

TABLE 24.4

FETAL ANATOMIC DEFECTS AND ASSOCIATED EFFECTS ON DEVELOPMENT

Anatomic Defect	Effect on Fetal Development
Congenital cystic adenomatoid malformation	Pulmonary hypoplasia Hydrops fetalis
Sacrococcygeal teratoma	High-output cardiac failure Hydrops fetalis
Laryngeal atresia/ congenital high airway obstruction syndrome	Pulmonary hypoplasia Hydrops fetalis
Twin-to-twin transfusion syndrome	Vascular steal Growth restriction (donor) High-output cardiac failure (donor) Hydrops fetalis (recipient) Hypertrophic cardiomyopathy (recipient) Pulmonary hypertension (recipient twin)
Twin reversed arterial perfusion	Vascular steal Hydrops fetalis Hypertrophic cardiomyopathy Note: all effects on "pump" twin
Myelomeningocele	Paraplegia Hydrocephalus
Lower urinary tract obstruction	Renal dysplasia Pulmonary hypoplasia (due to oligohydramnios) Deformation of distal extremities and facies (due to oligohydramnios)
Congenital diaphragmatic hernia	Pulmonary hypoplasia Pulmonary hypertension
Aortic stenosis	Hypoplastic left heart

TABLE 24.5

CURRENT RESEARCH ACTIVITY

Study Title	Location
Fetal intervention for aortic stenosis and evolving HLHS • Fetal aortic valvuloplasty	UCSF Fetal Treatment Center, San Francisco, CA
Standardized prenatal clinical care for LUTO • Fetal intervention for LUTO	Texas Children's Hospital-Pavilion for Women, Houston, TX
Fetal cystoscopy for severe LUTO • Cystoscopy vs. VAS	Mayo Clinic Rochester, MN
TRAP intervention study: early vs. late intervention for TRAP • Early vs. late selective of TRAP mass	Children's Memorial Hermann Hospital, Houston, TX Universitaire Ziekenhuizen Leuven, Leuven, Belgium, and 12 other international sites

(*continued*)

TABLE 24.5

CURRENT RESEARCH ACTIVITY (*continued*)

Study Title	Location
Renal agenesis fetal therapy • Serial amnioinfusion with normal saline	Johns Hopkins Hospital, Baltimore, MD
RCT of FETO with a balloon vs. expectant management during pregnancy in fetuses with left-sided congenital diaphragmatic hernia and moderate pulmonary hypoplasia • Balloon placement for tracheal occlusion	Baylor College of Medicine and Texas Children's Hospital, Houston, TX Universitaire Ziekenhuizen Leuven, Leuven, Belgium, and nine other international sites
FETO in severe left CDH (CHOP-FETO) • Balloon placement for tracheal occlusion	Children's Hospital of Philadelphia, Philadelphia, PA
Pilot trial: FETO for CDH • Balloon placement for tracheal occlusion	Mayo Clinic, Rochester, MN
Extended criteria for fetal MMC repair • Criteria for open fetal repair	Children's Memorial Hermann Hospital, Houston, TX Fetal Center at UTHealth, Houston, TX
RCT comparing a conservative management and laser surgery (TTTS stage 1) • Laser surgery for TTTS stage 1	Assistance Publique—Hôpitaux de Paris, Paris, France Cincinnati Children's Hospital Medical Center, Cincinnati, OH Fetal Treatment Program of New England, Hasbro Children's Hospital, Providence, RI The Texas Fetal Center, Children's Memorial Hermann Hospital, University of Texas Medical School, Houston, TX, and seven other U.S. sites (not actively recruiting)

CDH, congenital diaphragmatic hernia; CHOP, Children's Hospital of Philadelphia; FETO, fetoscopic endoluminal tracheal occlusion; HLHS, hypoplastic left heart syndrome; LUTO, lower urinary tract obstruction; MMC, myelomeningocele; RCT, randomized controlled trial; TRAP, twin reversed arterial perfusion; TTTS, twin-to-twin transfusion syndrome; UCSF, University of California, San Francisco; VAS, vesicoamniotic shunt.

Note: For additional clinical trials in fetal therapy, please refer to https://www.clinicaltrials.gov

SUMMARY

The primary goal of this chapter has been to describe fetal treatment and, in particular, fetal surgery. As this field rapidly evolves, expands, and broadens the options for treatment, more neonatal healthcare professionals will be approached by both colleagues and patients with questions on fetal intervention, including surgery. In this redefined clinical milieu, neonatal nurses must have a basic understanding of this area of medicine, including its associated technology and perhaps even the new ethical considerations it poses. This chapter recognizes the critical, complex, and often difficult role nurse specialists fulfill in fetal treatment, acting as both patient advocate and fetal treatment team representative. The responsibilities are complex, and the nurse specialist who fulfills them must be able to weigh, balance, interpret, and act on a variety of issues from a multifaceted, informed perspective. This chapter, then, is an acknowledgment of the talent, intellect, skill, and compassion that nursing professionals bring to the field of fetal treatment.

CASE STUDY

■ **Identification of the Problem.** A 31-year-old gravida 3, para 1, currently at 23 to 2/7 weeks, whose singleton gestation is complicated by a fetal MMC. The patient's amniocentesis results revealed a normal karyotype (46XX).

■ Assessment: History and Physical Examination

- Past medical history: unremarkable
- Surgical history: none
- Obstetric history: full-term normal spontaneous vaginal delivery (NSVD) 2 years ago (healthy male), followed by early first trimester spontaneous abortion (SAB)
- Meds: prenatal vitamins, Claritin, 1,600 mcg folic acid
- Allergies: NKDA (no known drug allergies)
- Social history: works as an accountant; her husband (present at today's visit) is employed as a police officer
- Family history: the patient's cousin may have had spina bifida, but the patient is unsure and at present has not been able to obtain records

■ Review of Systems

- GENERAL REVIEW OF SYSTEMS: negative
- CONSTITUTIONAL: she is oriented to person, place, and time; vital signs are normal; she appears well developed and well nourished
- HEAD: normocephalic and atraumatic
- EYES: conjunctivae and extraocular movement are normal; pupils are equal, round, and reactive to light
- NECK: normal range of motion; neck supple
- CARDIOVASCULAR: normal rate, regular rhythm, normal heart sounds, and intact distal pulses
- PULMONARY/CHEST: effort normal and breath sounds normal
- ABDOMINAL: soft; bowel sounds are normal
- GENITOURINARY: uterus gravid
- MUSCULOSKELETAL: normal range of motion
- NEUROLOGIC: she is alert and oriented to person, place, and time, she has normal reflexes
- SKIN: skin is warm and dry
- PSYCHIATRIC: she has a normal mood and affect; her behavior is normal; judgment and thought content normal

■ Diagnostic Tests

1. Fetal echo: Structurally and functionally normal
2. Obstetric ultrasound: Appropriately grown fetus with normal amniotic fluid volume. A severe Chiari II malformation is noted;

there is ventriculomegaly measuring 17 mm on each side; the level of the defect is felt to be at L1 to L2, and there is also the finding of syringomyelia (syrinx). There is concern of no visible normal spinal cord below the level of the syrinx (just neural elements). The placenta is anterior, and the cervical length appears normal.

3. MRI: Small posterior fossa, and downward descent of the cerebellar tonsils down to the level of C4, and a lumbar MMC, consistent with Chiari II malformation. Abnormal T2 hyperintensity is noted in the spinal canal in the lower cervical region extending to the lower thoracic cord, concerning for syrinx.
4. Laboratory tests: B+, Rh positive, antibody screen negative; Hct = 42.3, Hgb = 13.5, rubella immune, VDRL (venereal disease research laboratory) negative, HBsAg negative, and chlamydia and gonorrhea negative

■ **Working Diagnosis.** Pregnancy complicated with fetus with MMC

■ Development of Management Plan

Counseling. Discussed maternal and paternal history, the diagnostic findings, and the potential management options. Reviewed the MOMS trial that studied prenatal versus postnatal repair of MMC (Adzick et al., 2011). Reviewed the benefits of prenatal MMC repair seen in that trial, particularly the 40% reduction in need for shunting (primary outcome). Discussed the secondary outcomes of a potential decrease in ambulatory deficits, such as the need for a brace, or other motor functions such as bladder and bowel control. Patients who underwent prenatal repair appeared to have a benefit equivalent to a two-level improvement in location of the lesion (e.g., deficits associated with a L2 lesion would potentially be closer to those normally seen with an L4 lesion). Discussed the risks of prenatal surgery, most significant of which are preterm birth and maternal risks such as those associated with a uterine hysterotomy.

Regarding Preterm Birth. Based on the MOMS trial results, there was an 80% incidence of preterm birth in patients who had the prenatal fetal surgery repair, compared with a 15% preterm birth in the nonsurgery or postnatal group. While this amounts to a fivefold higher risk of delivering preterm, if the patient elects prenatal surgery versus postnatal surgery, it is important to examine this more specifically by severity of the gestational age at the time of such a preterm birth. The greatest increased risk is in delivery under 30 weeks' gestation because in patients who elected to have a postnatal repair, there were no births under this gestational age, whereas 12.8% of patients who had the prenatal repair delivered at less than 30 weeks. Overall, statistically 45% of patients who undergo prenatal surgery deliver at less than 34 weeks, whereas only 5% of patients who have a postnatal repair deliver at less than 34 weeks.

Risk involving the hysterotomy is potentially high and necessitates close surveillance. Of the 76 patients analyzed in the first publication of the MOMS trial who had prenatal surgery, 35.5% had thinning or dehiscence of their hysterotomy scar. For this reason, it is imperative that patients who undergo prenatal surgical repair receive very close monitoring for contractions and are evaluated immediately if they complain of discomfort.

Other maternal risks include leakage of amniotic fluid through the hysterotomy site, which would lead to oligohydramnios and the potential need for long-term hospitalization for the remainder (or significant portions) of the pregnancy. For some patients, leakage of amniotic fluid is painful and inflammatory and leads to significant discomfort during the remainder of the pregnancy. Less common risks include other general operative risks such as bleeding, the need for blood transfusion, anesthetic complications, infection, blood clots, and complications resulting from any of the medications necessary to stabilize the patient postoperatively.

■ **Pregnancy Management Options.** Three management options:

The patient can elect to undergo a pregnancy termination. Legally this can be performed up to 24 weeks' gestation.

The patient can elect to have standard postnatal repair. It is recommended that she undergo elective cesarean delivery at 39 weeks' gestation in the same center prepared to offer postnatal MMC repair. Pregnancy recommendations are monthly growth scans antenatally as well as weekly NST beginning at 32 weeks.

The patient can elect to undergo prenatal repair. This would be scheduled prior to 26 weeks' gestation. If the patient is over 24 weeks' gestation at the time of surgery, there is the option of antenatal corticosteroids if she would choose to undergo an emergent cesarean delivery in the event of fetal distress. The patient understands that regardless of fetal status, she would have to have a cesarean delivery for this pregnancy (even in the event of an intrauterine fetal death [IUFD]), as the fresh scar cannot undergo labor. For the prenatal surgery she would need both regional anesthesia (epidural) and general anesthesia. In the immediate postoperative period, the patient would be on IV magnesium and indomethacin. Once she no longer needed magnesium, the patient would begin oral nifedipine, which would continue until delivery. The usual postoperative course ranges between 4 and 5 days of inpatient hospitalization, followed by 2 to 3 weeks of local outpatient follow-up. If the patient has an uncomplicated outpatient postoperative course, she may be cleared to return home under the direct management of a perinatologist. Written guidelines for pregnancy management would be provided. Most importantly, as noted earlier, the patient should not be allowed to tolerate significant contractions or labor. She would need to be retocolyzed in the event of preterm labor and delivered by cesarean section if labor was unstoppable. Preterm premature rupture of membranes (PPROM), in the absence of contractions, can be managed as per usual protocol. Barring any other complications, the patient would have to undergo cesarean delivery by 37 weeks.

Regarding future pregnancies: There is no increased risk of infertility. There is also no option of vaginal birth after cesarean section, and all future pregnancies should be managed similar to having had a prior *classical scar* and should be delivered by early cesarean section. After a pregnancy involving a prenatal MMC repair, the uterus has a double scar (prenatal surgical hysterotomy plus delivery hysterotomy), which increases her risk in future pregnancies. It is advised that the patient adhere to a minimum interpregnancy interval of 16 months, and that, due to the double scar, future pregnancies be delivered at 36 weeks by repeat cesarean.

■ **Outcome.** Patient elected prenatal repair of fetal MMC. Surgery was performed the following week.

EVIDENCE-BASED PRACTICE BOX

Based on its most recent statistics, the Centers for Disease Control and Prevention (CDC, 2018) reports that birth defects affect 1 in 33 babies and are the leading cause of infant mortality in the United States, more so than low birth weight and prematurity, sudden infant death syndrome (SIDS), and maternal complications. Affected babies who survive are at increased risk for developing lifelong physical and cognitive challenges. Lifelong costs associated with birth defects, for example, and annual hospital stays are a significant stressor on families and the healthcare system alike. Fortunately, advances in fetal diagnosis allow clinicians to both accurately identify most complex anomalies prenatally and, more often, stratify the severity of the birth defect. In many instances, because diagnosis can be made in the second trimester, clinicians can provide families information that enables them to make more informed decisions about the pregnancy and the delivery plan and to plan and prepare for the future.

Over the past four decades, fetal intervention for congenital anomalies has evolved from a mere concept to a full-fledged medical specialty. The strategy of fetal intervention is to ameliorate or reverse some of the progressive physiologic organ damage that occurs from a particular defect. Operative techniques used in fetal surgery, such as open hysterotomy, fetal endoscopy, and image-guided percutaneous procedures, were developed and tested extensively in animal models first, before clinical application. These advances in surgical techniques paralleled and complemented those in fetal imaging, prenatal diagnosis, and maternal tocolysis. In a relatively short time, fetal intervention has become an important option for the treatment of fetuses who would otherwise not survive gestation or who would endure significant morbidity and mortality after birth.

The evolution of fetal surgery from research hypothesis to medical specialty was not without many trials and tribulations. The fetal therapy community quickly learned that justification for in-utero intervention based on anecdotal experience and retrospective studies of registry data was insufficient. Prospective controlled trials to determine the safety and efficacy of fetal interventions were necessary. As a result, in the mid-1990s, UCSF conducted the first NIH-sponsored trial examining open fetal surgical repair for CDH without herniated liver (Harrison et al., 1997). Upon completion of the trial, data suggested that fetal surgery for CDH, although physiologically sound and technically feasible, did not improve survival over standard postnatal treatment.

Three trends have dominated the field of fetal surgery. First, an emphasis has been placed on prospective RCTs instead of retrospective clinical trials to determine efficacy and effectiveness. The evolution of the interventions themselves represents a strategic shift from anatomic repair of a congenital anomaly to physiologic manipulation of the developmental consequences (e.g., from open in-utero repair of the diaphragmatic defect in CDH to temporary tracheal occlusion to promote lung growth). Finally, innovation in techniques represents a movement toward developing minimally invasive procedures. These overarching themes emphasize the objective of a multidisciplinary team of obstetricians, surgeons, perinatologists, nurses, anesthesiologists, and sonologists to promote maternal safety while improving outcomes for patients with fetal anomalies.

Many fetal treatment centers around the world have and are conducting clinical trials for fetal intervention. These centers have formed a cooperative and collaborative global community committed to reporting outcomes from fetal intervention, whether good or poor. These collaborations have already resulted in the successful completion of multicenter RCTs for TTTS and MMC. It is the dedication of these multidisciplinary teams that has helped establish fetal surgery as a medical specialty.

Prenatal screening, genetic testing, and improved imaging capabilities provide families more information earlier in their pregnancy. Potential parents are often not prepared for a poor prenatal diagnosis. Understandably, they react with fear and grief. All involved subspecialties have a very important, defined role. Clinicians have both the privilege and an ethical obligation to deliver services to families by educating parents about all their options, supporting them through the decision-making process, providing appropriate informed consent, and delivering competent and compassionate care. Providing care and support to the family faced with this news is of concern to all nurses who participate in their care. Nurses can be key planners/coordinators in the multidisciplinary team and have great potential to facilitate a healing environment for families facing the unexpected.

References

Center of Disease Control and Prevention (2018). *Data and statistics on birth defects*. Retrieved from https://www.cdc.gov/ncbddd/birthdefects/data.html

Harrison, M. R., Adzick, N. S., Bullard, K. M., Farrell, J. A., Howell, L. J., Rosen, M. A., … Filly, R. A. (1997). Correction of congenital diaphragmatic hernia in utero VII: A prospective trial. *Journal of Pediatric Surgery, 32*(11), 1637–1642. doi:10.1016/S0022-3468(97)90472-3

PARENT VOICES

Crystal Duffy

When I think back on the fetal surgery performed to save my babies' lives prior to their birth, I think of how blessed I was not only to live in a time with these advanced medical technologies but also lucky to have been geographically close to one of the few centers in the country specializing in twin-to-twin transfusion syndrome.

I attribute my babies' successful fetal surgery to advanced medical technology, dedication from a team of talented surgeons, and the faith and hope from both parents.

ONLINE RESOURCES

Advanced Fetal Care Center at Boston Children's Hospital. Retrieved from http://www.childrenshospital.org/centers-and-services/programs/a-_-e/advanced-fetal-care-center-program

The Center for Fetal Diagnosis and Treatment at Children's Hospital of Philadelphia. Retrieved from https://www.chop.edu/centers-programs/center-fetal-diagnosis-and-treatment

Cincinnati Fetal Center. Retrieved from http://www.cincinnatichildrens.org/service/f/fetal-care/services/surgical/default

Colorado Fetal Care Center. Retrieved from https://www.childrenscolorado.org/doctors-and-departments/departments/colorado-fetal-care-center/

The Fetal Center at Vanderbilt. Retrieved from http://www.childrenshospital.vanderbilt.org/fetalcenter

Fetal Health Center. Retrieved from https://www.childrensmercy.org/departments-and-clinics/fetal-health-center/fetal-surgery-and-intervention/

The Fetal Treatment Center at University of California, San Francisco. Retrieved from http://fetus.ucsf.edu

International Fetal Medicine and Surgery Society. Retrieved from http://ifmss.org

The Johns Hopkins Center for Fetal Therapy. Retrieved from https://www.hopkinsmedicine.org/gynecology_obstetrics/specialty_areas/fetal_therapy/index.html

Maternal Fetal Medicine at Children's Hospital of Michigan. Retrieved from https://www.childrensdmc.org/our-services/neonatal-and-perinatal-medicine/maternal-fetal-medicine

North American Fetal Therapy Network. Retrieved from https://www.naftnet.org

Texas Children's Fetal Center. Retrieved from https://women.texaschildrens.org/program/texas-childrens-fetal-center

REFERENCES

Adzick, N. S., Thom, E. A., Spong, C. Y., Brock, J. W., Burrows, P. K., Johnson, M. P., . . . Farmer, D. L. (2011). A randomized trial of prenatal versus postnatal repair of myelomeningocele. *New England Journal of Medicine, 364*(11), 993–1004. doi:10.1056/NEJMoa1014379

Al-Refai, A., Ryan, G., & Van Mieghem, T. (2017). Maternal risks of fetal therapy. *Current Opinion in Obstetrics and Gynecology, 29*, 80–84. doi:10.1097/GCO.0000000000000346

American College of Obstetricians and Gynecologists Committee on Ethics & American Academy of Pediatrics Committee on Bioethics. (2011). Maternal-fetal intervention and fetal care centers. *Pediatrics, 128*(2), e473–e478. doi:10.1542/peds.2011-1570

Bouchard, S., Johnson, M. P., Flake, A. W., Howell, L. J., Myers, L. B., Adzick, N. S., & Crombleholme, T. M. (2002). The EXIT procedure: Experience and outcome in 31 cases. *Journal of Pediatric Surgery, 37*(3), 418–426. doi:10.1053/jpsu.2002.30839

Clayton, D. B., & Brock, J. W. (2014). Lower urinary tract obstruction in the fetus and neonate. *Clinics in Perinatology, 41*(3), 643–659. doi:10.1016/j.clp.2014.05.012

Cozzi, F., Schiavetti, A., Zani, A., Spagnol, L., Totonelli, G., & Cozzi, D. A. (2008). The functional sequelae of sacrococcygeal teratoma: A longitudinal and cross-sectional follow-up study. *Journal of Pediatric Surgery, 43*(4), 658–661. doi:10.1016/j.jpedsurg.2007.10.066

Crombleholme, T. M. (2003). The treatment of twin-twin transfusion syndrome. *Seminars in Pediatric Surgery, 12*(3), 175–181. doi:10.1016/S1055-8586(03)00028-3

De Lia, J. D., Kuhlmann, R. S., Harstad, T. W., & Cruikshank, D. P. (1995). Fetoscopic laser ablation of placental vessels in severe previable twin-twin transfusion syndrome. *American Journal of Obstetrics and Gynecology, 172*(4), 1202–1211. doi:10.1016/0002-9378(95)91480-3

Deprest, J. A., Flake, A. W., Gratacos, E., Ville, Y., Hecher, K., Nicolaides, K., … Harrison, M. R. (2010). The making of fetal surgery. *Prenatal Diagnosis, 30*, 653–667. doi:10.1002/pd.2571

Deprest, J., Jani, J., Gratacos, E., Vandecruys, H., Naulaers, G., Delgado, J., … Nicolaides, K. (2005). Fetal intervention for congenital diaphragmatic hernia: *The European experience. Seminars in Perinatology, 29*, 94–103. doi:10.1053.j.semperi.2005.04.006

Derderian, S. C., Coleman, A. M., Jeanty, C., Lim, F. Y., Shaaban, A. M., Farrell, J. A., . . . Lee, H. (2015). Favorable outcomes in high-risk congenital pulmonary airway malformations treated with multiple courses of maternal betamethasone. *Journal of Pediatric Surgery, 50*, 515–518. doi:10.1016/j.jpedsurg.2014.08.019

Derderian, S. C., Iqbal, C. W., Goldstein, R., Lee, H., & Hirose, S. (2014). Fetoscopic approach to amniotic band syndrome. *Journal of Pediatric Surgery, 49*, 359–362. doi:10.1016/j.jpedsurg.2013.05.013

Duron, V. D., Watson-Smith, D., Benzuly, S. E., Muratore, C. S., O'Brien, B. M., Carr, S. R., & Luks, F. I. (2014). Maternal and fetal safety of fluid-restrictive general anesthesia for endoscopic fetal surgery in monochorionic twin gestations. *Journal of Clinical Anesthesia, 26*(3), 184–190. doi:10.1016/j.jclinane.2013.10.010

Euser, A. G., Meyers, M. L., Zaretsky, M. V., & Crombleholme, T. M. (2016). Comparison of congenital pulmonary airway malformation volume ratios calculated by ultrasound and magnetic resonance imaging. *The Journal of Maternal-Fetal & Neonatal Medicine, 29*(19), 3172–3177. doi:10.3109/14767058.2015.1118038

Farmer, D. L., Thom, E. A., Brock, J. W., Burrows, P. K., Johnson, M. P., Howell, L. J., … Adzick, N. S. (2018). The Management of Myelomeningocele Study: Full cohort 30-month pediatric outcomes. *American Journal of Obstetrics and Gyneocology, 218*(2), 256.e1–256.e13. doi:10.1016/j.ajog.2017.12.001

Graves, C. E., Harrison, M. R., & Padilla, B. E. (2017). Minimally invasive fetal surgery. *Clinics in Perinatology, 44*(4), 729–751. doi:10.1016/j.clp.2017.08.001

Haeri, S. (2015). Fetal lower urinary tract obstruction (LUTO): A practical review for providers. *Maternal Health, Neonatology and Perinatology, 1*(1), 26. doi:10.1186/s40748-015-0026-1

Harrison, M. R., & Adzick, N. S. (1993). Fetal surgical techniques. *Seminars in Pediatric Surgery, 2*(2), 136–142.

Hedrick, H. L., Flake, A. W., Crombleholme, T. M., Howell, L. J., Johnson, M. P., Wilson, R. D., & Adzick, N. S. (2005). The ex utero intrapartum therapy procedure for high-risk fetal lung lesions. *Journal of Pediatric Surgery, 40*(6), 1038–1044. doi:10.1016/j.jpedsurg.2005.03.024

Hedrick, H. L., Flake, A. W., Crombleholme, T. M., Howell, L. J., Johnson, M. P., Wilson, R. D., . . . Besner, G. (2004). Sacrococcygeal teratoma: Prenatal assessment, fetal intervention, and outcome. *Journal of Pediatric Surgery, 39*(3), 430–438. doi:10.1016/j.jpedsurg.2003.11.005

Hedrick, M. H., Ferro, M. M., Filly, R. A., Flake, A. W., Harrison, M. R., & Adzick, N. S. (1994). Congenital high airway obstruction syndrome (CHAOS): A potential for perinatal intervention. *Journal of Pediatric Surgery, 29*(2), 271–274. doi:10.1016/0022-3468(94)90331-X

Hirose, S., Farmer, D. L., Lee, H., Nobuhara, K. K., Harrison, M. R., Altman, R. P., . . . Cass, D. (2004). The ex utero intrapartum treatment procedure: Looking back at the EXIT. *Journal of Pediatric Surgery, 39*(3), 375–380. doi:10.1016/j.jpedsurg.2003.11.011

Hoagland, M. A., & Chatterjee, D. (2017). Anesthesia for fetal surgery. *Paediatric Anaesthesia, 27*(4), 346–357. doi:10.1111/pan.13109

Javadian, P., Shamshirsaz, A. A., Haeri, S., Ruano, R., Ramin, S. M., et al. (2013). Perinatal outcome after fetoscopic release of amniotic bands: a single-center experience and review of the literature. *Ultrasound in Obstetric & Gynecology, 42*, 449–455. doi:10.1002/uog.12510

Khalek, N., & Johnson, M. P. (2013). Management of prenatally diagnosed lung lesions. *Seminars in Pediatric Surgery, 22*(1), 24–29. doi:10.1053/j.sempedsurg.2012.10.005

Kiatano, Y. (1999). Open fetal surgery for life-threatening fetal malformations. *Seminars in Perinatology, 23*, 448–461. doi:10.1016/S0146-0005(99)80024-X

Laje, P., Johnson, M. P., Howell, L. J., Bebbington, M. W., Hedrick, H. L., Flake, A. W., & Adzick, N. S. (2012). Ex utero intrapartum treatment in the management of giant cervical teratomas. *Journal of Pediatric Surgery, 47*(6), 1208–1215. doi:10.1016/j.jpedsurg.2012.03.027

Lim, B. F., Crombleholme, T. M., Hedrick, H. L., Flake, A. W., Johnson, M. P., Howell, L. J., & Adzick, N. S. (2003). Congenital high airway

obstruction syndrome: Natural history and management. *Imaging, 38*(6), 940–945. doi:10.1016/S0022-3468(03)00128-33

Liu, J., Ye, Y., Dong, Z., Liu, Y., Ni, R., & Zheng, L. (2013). Anesthesia management for open fetal intrauterine surgery. *Clinical and Experimental Obstetrics and Gynecology, 40*(3), 403–406.

Macardle, C. A., Ehrenberg-Buchner, S., Smith, E. A., Dillman, J. R., Mychaliska, G. B., Treadwell, M. C., & Kunisaki, S. M. (2016). Surveillance of fetal lung lesions using the congenital pulmonary airway malformation volume ratio: Natural history and outcomes. *Prenatal Diagnosis, 36*(3), 282–289. doi:10.1002/pd.4761

McHugh, K., Afaq, A., Broderick, N., Gabra, H. O., Roebuck, D. J., & Elliott, M. J. (2010). Tracheomegaly: A complication of fetal endoscopic tracheal occlusion in the treatment of congenital diaphragmatic hernia. *Pediatric Radiology, 40*, 674–680. doi:10.1007/s00247-009-1437-9

McMann, C. L., Carter, B. S., & Lantos, J. D. (2014). Ethical issues in fetal diagnosis and treatment. *American Journal of Perinatology, 31*, 637–644. doi:10.1055/s-0033-1364190

Moldenhauer, J. S. (2013). Ex utero intrapartum therapy. *Seminars in Pediatric Surgery, 22*(1), 44–49. doi:10.1053/j.sempedsurg.2012.10.008

Moldenhauer, J. S., & Adzick, N. S. (2017). Fetal surgery for myelomeningocele: After the Management of Myelomeningocele Study (MOMS). *Seminars in Fetal and Neonatal Medicine, 22*(6), 360–366. doi:10.1016/j.siny.2017.08.004

Moon-Grady, A. J., Baschat, A., Cass, D., Choolani, M., Copel, J. A., Crombleholme, T. M., … Harrison, M. (2017). Fetal treatment 2017: The evolution of fetal therapy centers - A joint opinion from the International Fetal Medicine and Surgical Society (IFMSS) and the North American Fetal Therapy Network (NAFTNet). *Fetal Diagnosis and Therapy, 42*, 241–248. doi:10.1159/000475929

Mychaliska, G. B., Bealer, J. F., Graf, J. L., Rosen, M. A., Adzick, N. S., & Harrison, M. R. (1997). Operating on placental support: The ex utero intrapartum treatment procedure. *Journal of Pediatric Surgery, 32*(2), 227–231. doi:10.1016/S0022-3468(97)90184-6

Nassr, A. A., Erfani, H., Fisher, J. E., Ogunleye, O. K., Espinoza, J., Belfort, M. A., & Shamshirsaz, A. A. (2017). Fetal interventional procedures and surgeries: A practical approach. *Journal of Perinatal Medicine, 46*(7). doi:10.1515/jpm-2017-0015

Nassr, A. A., Shazly, S. A. M., Abdelmagied, A. M., Araujo Júnior, E., Tonni, G., Kilby, M. D., & Ruano, R. (2017). Effectiveness of vesicoamniotic shunt in fetuses with congenital lower urinary tract obstruction: An updated systematic review and meta-analysis. *Ultrasound in Obstetrics and Gynecology, 49*(6), 696–703. doi:10.1002/uog.15988

Noah, M. M. S., Norton, M. E., Sandberg, P., Esakoff, T., Farrell, J., & Albanese, C. T. (2002). Short-term maternal outcomes that are associated with the EXIT procedure, as compared with cesarean delivery. *American Journal of Obstetrics and Gynecology, 186*(4), 773–777. doi:10.1067/mob.2002.112249

Padilla, B. E., Vu, L., Lee, H., MacKenzie, T., Bratton, B., O'Day, M., & Derderian, S. (2017). Sacrococcygeal teratoma: Late recurrence warrants long-term surveillance. *Pediatric Surgery International, 33*(11), 1189–1194. doi:10.1007/s00383-017-4132-1

Partridge, E. A., Canning, D., Long, C., Peranteau, W. H., Hedrick, H. L., Adzick, N. S., & Flake, A. W. (2014). Urologic and anorectal complications of sacrococcygeal teratomas: Prenatal and postnatal predictors. *Journal of Pediatric Surgery, 49*(1), 139–143. doi:10.1016/j.jpedsurg.2013.09.042

Peralta, C. F. A., Jani, J. C., Van Schoubroeck, D., Nicolaides, K. H., & Deprest, J. A. (2008). Fetal lung volume after endoscopic tracheal occlusion in the preduction of postnatal outcome. *American Journal of Obstetrics and Gynecology, 198*, 60.e1–60.e5. doi:10.1016/j/ajog.2007.05.034

Peranteau, W. H., Adzick, N. A., Boelig, M. M., Flake, A. W., Hedrick, H. L., Howell, L. J., . . . Johnson, M. P. (2015). Thoracoamniotic shunts for the management of fetal lung lesions and pleural effusions: A single-institution review and predictors of survival in 75 cases. *Journal of Pediatric Surgery*, 50, 301–305. doi:10.1016/j.jpedsurg.2014.11.019

Peranteau, W. H., Boelig, M. M., Khalek, N., Moldenhauer, J. S., Martinez-Poyer, J., et al. (2016). Effect of single and multiple courses of maternal betamethasone on prenatal congenital lung lesion growth and fetal survival. *Journal of Pediatric Surgery, 51*, 28–32. doi:10.1016/j.jpedsurg.2015.10.018

Peranteau, W. H., Moldenhauer, J. S., Khalek, N., Martinez-Poyer, J. L., Howell, L. J., Johnson, M. P., . . . Hedrick, H. L. (2014). Open fetal surgery for central bronchial atresia. *Fetal Diagnosis and Therapy, 35*(2), 141–147. doi:10.1159/000357497

Pogoriler, J., Swarr, D., Kreiger, P., Adzick, N. A., & Peranteau, W. H. (2019). Congenital cystic lung lesions: Redefining the natural distribution of subtypes and assessing the risk of malignancy. *The American Journal of Surgical Pathology, 43*(1), 47–55. doi:10.1097/PAS.0000000000000992.

Quintero, R. A., Morales, W. J., Allen, M. H., Bornick, P. W., Johnson, P. K., & Kruger, M. (1999). Staging of twin-twin transfusion syndrome. *Journal of Perinatal Medicine, 19*(8), 550–555. doi:10.1038/sj.jp.7200292

Rintoul, N., Ades, A., Adzick, N. S. (2018). Fetal Therapy. In M. W. Kline (Ed.). *Rudolph's pediatrics* (23rd ed.). New York, NY: McGraw-Hill Education.

Ryan, G., Somme, S., & Crombleholme, T. M. (2016). Airway compromise in the fetus and neonate: Prenatal assessment and perinatal management. *Seminars in Fetal and Neonatal Medicine, 21*(4), 230–239. doi:10.1016/j.siny.2016.03.002

Saracoglu, A., Saracoglu, K. T., Alatas, I., & Kafali, H. (2015). Secrets of anesthesia in fetoscopic surgery. *Trends in Anaesthesia and Critical Care, 5*(6), 179–183. doi:10.1016/j.tacc.2015.10.004

Saracoglu, A., Saracoglu, K. T., & Kafali, I. H. (2016). The importance of maintaining an optimal hemodynamic state during minimally invasive fetal surgery. *Journal of Clinical Anesthesia, 34*, 365–366. doi:10.1016/j.jclinane.2016.05.017

Senat, M.-V., Deprest, J., Boulvain, M., Paupe, A., Winer, N., & Ville, Y. (2004). Endoscopic laser surgery versus serial amnioreduction for severe twin-to-twin transfusion syndrome. *New England Journal of Medicine, 351*(2), 136–144. doi:10.1056/NEJMoa032597

Titus, M. J. & Moodley, J. (2012). Advances in fetal genetic diagnosis and therapy: Ethical issues and appropriate technology in cost-restrained countries. *Best Practice & Research Clinical Obstetrics and Gynecology, 26*, 531–540. doi:10.1016/j.bpobgyn.2012.06.004

Tulipan, N., Wellons, J. C., Thom, E. A., Gupta, N., Sutton, L. N., Burrows, P. K., … Adzick, N. S. (2015). Prenatal surgery for myelomeningocele and the need for cerebrospinal fluid shunt placement. *Journal of Neurosurgery: Pediatrics, 16*(6), 613–620. doi:10.3171/2015.7.PEDS15336

Upadhyaya, M., & Lander, A. (2013). Advances in fetal surgery. *Surgery (United Kingdom), 31*(3), 114–118. doi:10.1016/j.mpsur.2013.01.009

Van Mieghem, T., Al-Ibrahim, A., Deprest, J., Lewi, L., Langer, J. C., Baud, D., . . . Ryan, G. (2014). Minimally invasive therapy for fetal sacrococcygeal teratoma: Case series and systematic review of the literature. *Ultrasound in Obstetrics and Gynecology, 43*(6), 611–619. doi:10.1002/uog.13315

Victoria, T., Danzer, E., & Adzick, N. S. (2013). Use of ultrasound and MRI for evaluation of lung volumes in fetuses with isolated left congenital diaphragmatic hernia. *Seminars in Pediatric Surgery, 22*(1), 30–36. doi:10.1053/j.sempedsurg.2012.10.006

Wenstrom, K. D., & Carr, S. R. (2014). Fetal surgery: Principles, indications, and evidence. *Obstetrics and Gynecology, 124*(4), 817–835. doi:10.1097/AOG.0000000000000476

Wu, S., & Johnson, M. P. (2009). Fetal lower urinary tract obstruction. *Clinics in Perinatology, 36*(2), 377–390. doi:10.1016/j.clp.2009.03.010

Yao, W., Li, K., Zheng, S., Dong, K., & Xiao, X. (2014). Analysis of recurrence risks for sacrococcygeal teratoma in children. *Journal of Pediatric Surgery, 49*(12), 1839–1842. doi:10.1016/j.jpedsurg.2014.09.036

CHAPTER 25

Surgical Considerations in the Newborn and Infant

Kaye Spence

INTRODUCTION

Caring for an infant with a surgical condition is an exciting challenge that requires knowledge of pathophysiology and current neonatal care practices, training to recognize and respond to complications, and an ability to extend supportive care to the family. Optimum outcome is achieved through the skills of a multidisciplinary team that includes neonatal nurses, neonatologists, pediatric surgeons, radiologists, anesthesiologists, respiratory therapists, and parents. The members of this team must work together, guided by the knowledge that all principles of neonatal care, as well as additional considerations related to surgical care, apply in each case. This chapter outlines the special considerations of the newborn infant who undergoes surgical procedures in the newborn period and shortly after.

ANTENATAL CONSIDERATIONS

Neonatal surgery has been inextricably linked to the field of obstetrics with neonatologists and surgeons, along with fetal medicine specialists, obstetricians, and midwives working together to characterize the development and well-being of fetuses with congenital malformations (Cass, 2011). Many congenital surgical defects are diagnosed in utero through routine prenatal screening, providing time for education and emotional support for the family. Women are transferred to a high-risk birth unit with skilled fetal–maternal specialists with access to a neonatal surgeon. If possible, a tour of the neonatal intensive care unit (NICU) should be arranged before delivery for the prospective parents as meeting the team and knowing their roles can help reduce a parent's anxiety (Wilpers, Kennedy, Wall, Funk, & Bahtiyar, 2017). It is recommended that the parents meet with members of the surgical and neonatal teams to discuss the findings and probable prognosis for their infant. Information given to the family should include the natural history of the abnormality, timing of surgery, anticipated surgical outcomes, possible long-term sequelae, and any other possible problems that may be involved with the neonate's course (Lakhoo, 2012). There have been many changes over the past decades in the care and management of newborn infants requiring surgery. Important areas of advancement have been in newborn intensive care and postoperative care. Another area of advancement has been in antenatal diagnosis and the early referral to NICUs for information and education regarding the expected course of treatment and the outcomes of surgical care for newborn infants. For more information on fetal surgery, please see Chapter 24, Fetal Therapy.

TRANSPORTATION OF INFANTS FOR SURGERY

Infants requiring surgery should be born in an appropriate tertiary perinatal center, adjacent to pediatric surgical facilities, in accordance with best practice. Pregnancies complicated by birth defects have variable rates of antenatal diagnosis and may require surgical repair in the newborn period. The success of antenatal transfer is dependent on the complexity of the antenatal diagnosis, and with regionalization of maternal and neonatal services the healthcare of women outside specific urban areas are not disadvantaged. For some specific conditions, such as congenital heart disease, transferring the mother for delivery to a high-risk center is preferred (Calisti et al., 2012) so that an expedited transfer from the birth unit to the NICU can occur in a matter of minutes. Advantages of antenatal referral of infants with congenital anomalies requiring surgery include:

1. Improved neonatal outcomes
2. The opportunity for parents to discuss the following issues with experienced staff:
   - Options for birth
   - Anticipated care of the baby
   - Likely neonatal outcomes
3. The reassurance of access to the best available obstetric and neonatal care
4. Women may also experience a reduction in stress and anxiety as an emergency transfer of the baby resulting in separation of mother and baby is avoided (Wilpers et al., 2017).

Approximately 80% of neonates with an antenatal diagnosis of a congenital anomaly require admission to a NICU and major surgery. Emergency transport services retrieve neonates to tertiary referral centers for intensive care, diagnostic workup, or surgery. If birth occurs at an appropriate tertiary perinatal center, the potential for an emergency neonatal retrieval to a pediatric facility is avoided. The mortality rate is falling for neonates who have surgery in the first 28 days (Tauro, Walker, Halliday, Jatana, & Trivdi, 2018).

It is desirable for each maternity unit to have a policy on antenatal referral of mothers with babies known to have a congenital

abnormality, likely one that would require surgery. The policy should emphasize antenatal consultation with the appropriate fetal, surgical, and other consultants (e.g., genetics, cardiac) in the preferred facility. It should note that the decision to make an antenatal maternal referral should take into account patient and clinician preferences. The policy should include options and processes for antenatal referral for more detailed fetal assessment and a plan for the optimal place of delivery. This referral will usually occur in mid-pregnancy. **Quality and Safety: If surgery or other critical therapy is likely to be required soon after birth, this plan should include delivery at a perinatal center with direct access to appropriate pediatric surgical services.** For women in nonurban locations, transfer to a tertiary care centre around 34 weeks' gestation may be desirable.

SURGICAL NEONATAL INTENSIVE CARE UNITS

Criteria for neonatal surgical units have been established in several countries to ensure that acceptable standards are met for infants who require surgery during the neonatal period. There are identified requirements for surgical services that provide operations and general anesthesia for newborn infants. These requirements relate to adequate training for the consultant surgeon and anesthetist with sufficient caseloads to maintain skills (McAteer et al., 2013). In addition, adequately trained and experienced staff to care for the infant postoperatively need to be available in dedicated newborn surgical units.

There are arguments for and against large regional specialist pediatric centers being established for neonatal surgery. Benefits of regionalization include pooling of expertise, appropriate consultants, support services, and staff training. Disadvantages include children and their families having to travel long distances for care and the loss of expertise at a local level. However, the availability of a neonatal emergency transport service can provide expertise and support for transferring neonates to regional neonatal surgical intensive care centers (Fullerton et al., 2016).

There are trends in some countries to ensure that surgical neonatal intensive care units (SNICUs) are located in children's hospitals with a co-located perinatal center. This practice enables the women to deliver with a high-risk obstetric team as well as having a specialist pediatric/neonatal surgical team present to attend to the infant's well-being.

Staffing

The majority of the nursing staff in SNICUs require skills and competence in neonatal intensive care as well as the specific management of neonatal surgical patients. Recommendations for staffing ratios vary; however, most infants will require dedicated nursing staff in the immediate postoperative period. During this period many infants will be unstable, and vigilant observation and assessment are required to avert postoperative complications. In addition, the families require additional support and explanation of many of the unique procedures seen in infants who have undergone surgery. A dedicated in-service program that includes a multidimensional approach to various conditions, altered pathophysiology, care paths, techniques, and procedures as well as counseling skills is recommended (Gallagher, 2013). A wide range of subspecialists, including cardiologists, gastroenterologists, endocrinologists, geneticists, infectious disease specialists, respiratory specialists, and anesthetists, as well as allied health professionals, are involved in the SNICU; this requires a coordinated effort of team meetings and communication. Nurses are in key positions to coordinate the information and develop care plans to ensure continuity when multiple specialist teams are involved. The combined skills of the pediatric surgeon, pediatric anesthetist, neonatologist, and neonatal nurse together with the resources available in a regional pediatric center will continue to contribute to the improvements in survival and quality of life of infants requiring neonatal surgery. However, there does need to be continuing debate on the surgical advances for infants with congenital malformations. Issues such as long-term outcomes and future quality of life need to be considered by the team together with the families. Other issues such as resources and cost-effectiveness of the treatments need to be part of the community debate for future healthcare programs; according to present evidence, neonatal surgery yields good value for money and contributes to equity in health.

Family

Families will seek out information about their infant's prenatally diagnosed condition (Usui, Kamiyama, Tani, Kanagawa, & Fukuzawa, 2011) and require open and honest communication from the healthcare team regarding prognosis, treatment options, and outcomes. Decisions on the management and treatment of the infant require a team approach that includes parents, nurses, obstetricians, pediatric surgeons, neonatologists, nurse practitioners, and radiologists. Supportive services should be provided to the family as indicated to reduce some of the stressors of having their newborn infant undergo surgery (Diffin, Spence, Johnston, & Badawi, 2012). Providing opportunities for kangaroo care prior to the operation may help alleviate some stressors and it has been shown that with an opportunity to breastfeed prior to surgery can improve breastfeeding rates postoperatively for cardiac infants (McKean et al., 2017).

Parents want comprehensive information, especially during the waiting periods. Parental coping may be greatly enhanced by timely updates from the operating room (OR) while the parents are waiting for their infant in surgery. It is also important for the surgeon to speak with the parents immediately after surgery to discuss findings and the infant's condition. Once the infant is back from the OR, the parents are encouraged to visit in a timely manner to reduce anticipatory stress. The nurse will discuss the infant's current condition, the equipment used, and anticipatory care in the short term.

In the postoperative period, parents need to be able to negotiate their parental role with the staff members caring for their infant and are supported in their attempts to advocate for their infant. Parents are also encouraged to participate in their child's care to the extent that it is comfortable for them. This participation means that parents must be provided with adequate information and guidance regarding their role to enable them to cope and use informal support structures to help allay their anxiety (McFadyen et al., 2011).

CLASSIFICATION OF NEONATAL SURGERY

Neonatal surgery is defined as surgery performed on infants who

- Are less than 28 days old
- Weigh less than 2,500 g regardless of age
- Require care in a NICU regardless of age or weight

Approximately 0.6% of newborn infants undergo surgery in the first 4 weeks of life (Badawi et al., 2003). Some of the most common types of surgical procedures performed are gastrointestinal, cardiovascular, hernia, genitourinary, and neurosurgical.

Neonatal surgery can be classified into three groups for ease of management. Group 1 includes those infants with a life-threatening

condition for whom a surgical operation is necessary within the first day of life, such as congenital diaphragmatic hernia, gastroschisis, or esophageal atresia with fistula and critical congenital cardiac malformations. In group 2 are those infants with an obvious abnormality but for whom a surgical operation may be deferred for days or months, such as exomphalos minor or cleft lip. Group 3 includes infants who have an obvious abnormality whose management may consist of interventions after due consideration, such as myelomeningocele.

PREANESTHETIC EVALUATION

Anesthetizing a preterm or critically ill neonate requires constant vigilance, rapid recognition of events and trends, and swift intervention. The anesthetic considerations in the preterm neonate are based on the physiologic immaturity of the various body systems, the associated congenital disorders, and possible poor tolerance of anesthetic drugs and considerations regarding use of high concentrations of oxygen. The preoperative assessment should include consultation with the parents, including the description of postoperative respiratory support. A complete examination is undertaken, with special attention to the appearance of the upper airway and the possibility of difficult intubation (Taneja, Srivastava, & Saxena, 2012). Preterm and ex-premature infants can have dramatic responses with wide variability to narcotics and inhaled anesthetics.

Preoperative investigations include hemoglobin, hematocrit, and platelets, and the coagulation profile should be within acceptable limits. Serum electrolyte, glucose levels, arterial blood gas, and chest x-ray will aid in intraoperative management and stabilization (Taneja et al., 2012). A blood cross-match must be available so that a transfusion can be given if the blood loss exceeds 10% of blood volume during surgery.

PREPARATION FOR SURGERY

From the time of delivery, the goal is to reduce the likelihood of morbidity and mortality by continually assessing the infant and the responses to treatments instituted. Preparation for surgery starts with discussions with the family and gaining informed consent. The consent process is the responsibility of the surgical team; however, it is good practice for the nurse to be present when these discussions take place. If the parents are from a non–English-speaking background, then an interpreter needs to be present. Often nurses are asked to clarify issues that were discussed, and nurses are in a unique position to communicate misunderstandings back to the surgical team.

Quality and Safety: Many of the neonatal surgical procedures are performed on emergency operative lists; therefore, the preparation needs to be coordinated and the many teams involved aware of the infant's condition prior to surgery. The anesthetist holds a key role in this coordination with multiple subspecialists, and the nurse is pivotal in ensuring the documentation is complete and the family informed and available. Each institution needs to have a clear and comprehensive system of evaluating infants during the preoperative period to ensure effective use of operating time and to avoid undue delays and stress on the infant and family. An understanding of neonatal physiology is necessary to enable the team to provide appropriate care in three areas of homeostasis—temperature regulation, fluid and electrolyte balance, and acid–base balance (Taneja et al., 2012). In addition, specific practices for preparation for transfer to the OR are described in this chapter. Each area is discussed in relation to the preparation of the infant for surgery.

Temperature Management

Heat loss can occur during transfer to the imaging department and the OR due to the infant's high ratio of surface area to body weight. It remains important to maintain the core body temperature close to 37°C to minimize oxygen consumption. In the OR, a low ambient temperature increases heat loss by both convection and radiation. It is ideal that the OR be warmed to 28°C to 30°C for neonatal patients. The infant may be transferred on an open-care bed with a radiant warmer and cover; some surgeons will operate on these beds to minimize the stress of heat loss. The infant undergoing surgical procedures where the organs are exposed is at particular risk of heat loss.

Quality and Safety: Prevention of hypothermia in the surgical neonate is imperative in the preoperative period. Maintaining a neutral thermal environment is a constant challenge. In a neutral thermal environment, metabolic activity is minimal because body temperature is kept stable. Oxygen consumption is reduced, and acidosis is prevented. Any prolonged deviations from the neutral thermal environment further stress the infant's already limited thermoregulatory abilities. Strategies such as wrapping the infant's head and limbs in cotton webbing can be useful in reducing some of the inevitable heat loss.

Heat loss occurs through evaporation, conduction, convection, and radiation. Evaporative heat loss occurs with exposure of the intestinal contents of a ruptured omphalocele or gastroschisis. In the case of an encephalocele or a myelomeningocele, the unprotected spinal cord may allow heat loss. The exposed bladder mucosa in exstrophy of the bladder also contributes to heat loss. This type of heat loss can be prevented by applying warm dressings to the defects and then covering these areas with plastic wrap. Do not use saline-soaked dressings as this can add to the evaporative heat loss.

Conductive heat loss occurs with direct skin contact with a cold surface, such as cold or wet linens, an operating table, radiographic plates, or an unwarmed bed. To prevent this type of heat loss, linens should be prewarmed as the bed or incubator is warmed. Operating or radiography tables can be warmed with heat lamps before and during procedures. Linens that become wet should be replaced with dry, warmed linens; radiographic plates and scales should be covered with warmed linens before the infant is placed on them.

Heat loss by convection occurs when air blows over the infant. Use of warmed oxygen in head hoods (boxes) and ventilators can reduce this type of heat loss. Also, it is essential that the incubator door not be open for prolonged periods. Insertion of nasogastric tubes, placement of intravenous lines, radiographic studies, physical examinations, and phlebotomy procedures should be performed through the incubator portholes to reduce heat loss. An additional heat source may be placed over the incubator when the door must be open.

Heat loss by radiation is the most difficult to control. This type of heat loss occurs during transportation of the neonate in cold hallways or in the cold OR. To prevent this cold stress, the infant should be covered with warmed linens or wrapped during transport. ORs should be prewarmed to well above the "comfortable" temperature. Nursing care that focuses on the thermoregulatory process of the neonate is vital to the prevention of complications related to poor temperature control. It is also beneficial to use warmed solutions for suctioning and dressing changes. Frequent monitoring of the infant's temperature is extremely important. Consistency in the method of measuring temperature and appropriate documentation are also essential.

Fluid and Electrolyte Balance

Adequate fluid volume is required to ensure the perfusion of all organ systems. An inadequate vascular volume interferes with the oxygen supply to peripheral tissues, resulting in cellular damage and acidosis. Precision in fluid management is essential; there is little margin for error. Particular care needs to be taken to ensure excessive volumes are not delivered with additional drugs used during the anesthesia. All fluid losses must be measured accurately to ensure adequate replacement. Estimation of insensible fluid losses is essential, including those caused by humidification through ventilation and radiant heating. Unexpected fluid losses and inadequate fluid replacement delay preoperative stabilization of the neonate's condition.

Infants with an esophageal atresia may have continuous losses of saliva suctioned from the esophageal pouch that needs to be considered in the fluid balance. The large exposed intestinal area seen with a ruptured omphalocele or gastroschisis results in large volumes of fluid losses. Replacement of these losses may involve up to twice the normal maintenance fluids of a neonate. If a membranous sac protects an omphalocele, the fluid requirement is less.

Gastrointestinal obstructions cause fluid losses from vomiting, aspiration, and the suctioning required for gastric decompression. Infants with open neural tube defects also have increased fluid losses. A leaking myelomeningocele requires increased fluid administration to keep up with the loss of cerebrospinal fluid.

Peritonitis, such as occurs with intestinal perforations in necrotizing enterocolitis, midgut volvulus, or ruptured meconium ileus, causes third spacing of fluid (capillary leak syndrome) or fluid shifts into the bowel, necessitating increased fluid replacement. Third spacing of fluids, or capillary leak syndrome, is the result of trauma to the gastrointestinal system. The capillary membrane's permeability is changed. This phenomenon may be due to natural fibronectin, a glycoprotein secreted by epithelial cells in the pulmonary and gastrointestinal trees. It is secreted in response to stimulation of the immune system to heal a wound. Fibronectin alters capillary permeability, shifting fluid and resulting in a "leaky capillary" and the third spacing of fluid. The body's compensatory response to any gastrointestinal trauma, then, can result in a movement of fluid across this "leaky" membrane. Fluid moves out of the vascular compartment and into the tissues, and the infant develops generalized edema. Abdominal swelling exerts pressure on the thoracic cavity, increasing the work of breathing. Gas exchange and ventilation are compromised as a result of (a) the pressure; (b) the decreased circulation; (c) the increased workload of the heart, which delivers oxygen to the tissues; and (d) the increasing loss of the buffer system through the mechanisms of diminished kidney perfusion and gastric losses.

The numerous conditions that affect the surgical neonate may result in imbalances of serum electrolytes, especially sodium and potassium. Fluid losses and inadequate intake result in hypokalemia and hyponatremia.

Hyperkalemia occurs with acidosis, excessive potassium intake, and renal failure. Renal failure may result from genitourinary obstructions or from sepsis and poor perfusion, as is seen with necrotizing enterocolitis with perforation or peritonitis.

The causes of hypernatremia are generally iatrogenic. An excessive intake of sodium occurs with the administration of hypertonic solutions, intravenous flushes with normal saline or heparinized normal saline, or sodium bicarbonate for treatment of acidosis. **Emergency Alert: Return to a fluid and electrolyte balance is needed to improve the neonate's ability to tolerate any necessary operative procedure and to reduce the likelihood of complications.**

Maintenance of Glucose Levels

Fluctuation in the glucose level is a major indication of stress and infection. Preoperative hyperglycemia can result from sepsis or excessive intravenous administration of glucose. Hypoglycemia may result from a multitude of problems. For example, reduced glycogen stores are seen in premature infants and in infants with intrauterine growth restriction. Excessive insulin production occurs in the infant of a diabetic mother and with sudden or prolonged cessation of glucose infusions, as may occur with difficult or delayed insertion of intravenous lines. Abnormalities in glucose metabolism are evident with sepsis, shock, and asphyxia, as well as with various central nervous system (CNS) abnormalities. **Emergency Alert: Glucose infusions must be carefully titrated to provide adequate hydration while the serum glucose is slowly restored to an acceptable concentration, avoiding extremes in the serum glucose level.**

Acid–Base Balance

A variety of factors can alter the acid–base balance in the surgical neonate. Major conditions that can result in acidosis include inadequate respiratory support and fluid or electrolyte imbalances. The effects of sepsis and tissue necrosis are also significant causes of acidosis. Acidosis in the surgical neonate can be of the respiratory, metabolic, or mixed type.

Respiratory acidosis could occur with decreased ventilation, resulting in an increased partial pressure of carbon dioxide (P_{CO_2}) and a decreased pH. An overproduction of acids may occur with any condition that causes a decrease in oxygenation or perfusion. Impaired kidney function, such as that which occurs in acute renal failure or renal tubular necrosis, reduces elimination of hydrogen ions, contributing to the development of metabolic acidosis. Bicarbonate losses are increased with severe diarrhea, intestinal fistulas, vomiting, and gastric drainage, resulting in metabolic acidosis.

Poor tissue perfusion causes acidosis, as is seen with multiple gastrointestinal anomalies that are accompanied by large fluid losses. These anomalies include tracheoesophageal fistula with esophageal atresia, ruptured omphalocele and gastroschisis, bowel obstruction, and necrotizing enterocolitis. Adequately replenishing fluid or blood volume usually corrects this metabolic acidosis. When necrosis or perforation occurs, however, the acidosis may not be correctable until the necrotic bowel has been removed and any resulting sepsis treated.

Drugs

The role of prophylactic antibiotics for neonatal surgery remains controversial. However, with suspected gastrointestinal obstruction, antibiotics may be needed to treat peritonitis or enterocolitis. The progression of necrotizing enterocolitis may be slowed with vigorous antibiotic therapy. Treatment of omphalocele and gastroschisis may include antibiotics to protect the exposed gastrointestinal contents and to help prevent ischemic injury to the abdominal contents. If pneumonia accompanies an esophageal atresia with tracheoesophageal fistula, aggressive antibiotic therapy may be instituted to clear the pneumonia and promote optimum surgical repair of the defect. The infant with a myelomeningocele requires antibiotic treatment to prevent meningitis.

Inotropic agents may be necessary to improve cardiac function and thus improve organ perfusion impaired by sepsis and stress. The most frequently used agents are dobutamine and dopamine. Dobutamine hydrochloride achieves organ perfusion by increasing cardiac output. Dopamine hydrochloride, used in low to moderate doses, causes vasodilation with resultant improvement in cardiac, renal, gastrointestinal, and cerebral blood flow. Use of dopamine

hydrochloride at high doses, however, causes vasoconstriction of renal and gastrointestinal vessels. This vasoconstriction could worsen the condition of a renal system affected by obstruction or poor flow status, as well as the gastrointestinal system already compromised by necrotizing enterocolitis, omphalocele, gastroschisis, or obstruction. **Emergency Alert: Doses of dobutamine hydrochloride and dopamine hydrochloride, therefore, must be carefully calculated and continually titrated to achieve the desired effect.** Furthermore, these medications are incompatible with many other drugs. For example, alkaline solutions (e.g., sodium bicarbonate, ampicillin, gentamicin, and furosemide) can inactivate dobutamine and dopamine. These inotropic agents are also irritating to vessels, and close monitoring of intravenous sites for infiltration is essential.

A buffering agent may be required to treat the acidosis that may accompany a diaphragmatic hernia, necrotizing enterocolitis, omphalocele, gastroschisis, or obstruction with resulting ischemic injury. Adequate ventilation and tissue perfusion must be established and maintained before medication is used to treat acidotic conditions.

Monitoring

Infants will require preoperative monitoring that continues during the operation into the postoperative period. At a minimum, cardiorespiratory monitoring is essential. The electrodes and leads should be placed with consideration of the operative area; this will enable the monitoring leads to be used during the surgery without the necessity of tissue damage from removal and re-siting. A pulse oximeter on an upper limb will enable the oxygen saturation levels to be monitored. The nurse needs to be mindful that some monitoring, such as transcutaneous oxygen, may be ineffective because of changes in skin perfusion during the procedure. The placement of a temperature probe can assist the anesthetist in monitoring the temperature during surgery. Amplitude electroencephalogram (aEEG) monitoring is recommended for neonates prior to surgery to aid in the postoperative course and as a way of determining cerebral insults that are possible during the anesthesia and surgery (Mehta, Hunt, Walker, & Badawi, 2016).

Intravascular Lines

Ideally, a central venous catheter (CVC) is placed to assist postoperatively for multiple drug infusions and parental nutrition (PN). It may be opportune for the CVC to be inserted during the operative procedure; this may be negotiated with the surgeon and anesthetist.

Quality and Safety: In addition, a peripheral arterial cannula is required for the continuing measurement of the acid–base balance during the operation and in the postoperative period. It is best if this is inserted before the infant is transferred to the OR. Precautions should be taken to ensure that all connections are Luer-Lok to avoid accidental disconnection when covered with surgical drapes. Emergency Alert: Caution needs to be taken if multiple drug infusions are required; incompatibilities and priority for access can be a challenge for complex conditions.

Nurse's Role

Adequate and thorough preparation of the infant can minimize stress during the process and help reduce the preparation and time of the surgery. Being prepared and anticipating the time and call for surgery can ensure that the infant is adequately prepared for transfer and surgery. If the nurse accompanies the infant to the OR, continued monitoring and a smooth handover can occur. In some institutions, the neonatal nurse can remain in the OR assisting the infant and helping with the monitoring of the oxygenation and temperature. This is, however, a contentious issue for some institutions and OR staff.

The prospective site of the surgery needs to be prepared through the use of an antiseptic wash prior to the transfer for surgery. In the case of a stoma formation, the stoma therapist will indicate on the infant's abdomen the preferred location for the stoma. This type of preparation can make the postoperative care easier and avoid undue stress for the infant from a leaking stoma bag due to poor location. The surgeon makes a mark to indicate the side (right or left) for the operation to avoid a potential mistake during the operation.

A Preoperative Checklist may be helpful in ensuring that all the relevant information is available (Box 25.1).

Box 25.1

PREOPERATIVE CHECKLIST

- Record infant's weight (both birth and current) and gestational age
- Determine that preoperative condition is stable and optimal
- Identify associated conditions such as heart or lung disease, renal abnormalities
- Review preoperative investigations
- Ensure that venous access has been established
- Ensure blood has been cross-matched and available
- Reassure the parents

DURING SURGERY

Anesthesia

The developing brain in neonates is susceptible to the possible neurotoxic effects of general anesthesia (Davidson & Sun, 2018). Other considerations that may contribute to neurodevelopmental outcomes include managing fluid, respiratory, cardiovascular, glucose, and pain responses to surgery. The timing of anesthesia needs to be considered and weighed in relation to the need for surgery and possible harmful effects, as the evidence in humans is yet to be determined.

The intraoperative period places the infant at risk of fluctuations in vital signs as well as stress. Many neonates will arrive at the OR already intubated and ventilated. The endotracheal tube needs to be secure to ensure that accidental extubation does not occur. This is the responsibility of the anesthetist, who may elect to re-intubate prior to the surgery.

The choice of anesthetic agent will depend on the type of operation, the defect, and the infant's status. Muscle relaxants are commonly used together with controlled ventilation and humidified gases for neonates. Inhalation anesthetic agents are commonly administered in 100% oxygen during the anesthesia, and the use of opioids can limit episodes of hypoxic pulmonary vasoconstriction. How infants are positioned during surgery can predispose them to hypoxia. For example, when positioned in the lateral decubitus position for thoracic surgery, infants are at significant risk of hypoxia due to their increased consumption of oxygen. Complications such as an elevated intrathoracic CO_2 pressure during thoracic surgery may lead to decreased cerebral oxygen saturation. The use of newer modes of monitoring such as cerebral oxygenation (near-infrared spectroscopy) and blood flow (cerebral Doppler) may be

warranted (Neunhoeffer et al., 2017). This type of information is useful when nurses are challenged to care for recovering infants in the postoperative period.

Anesthetic agents can cause respiratory depression, as can narcotic and sedative medications. The neonate has a limited capacity to tolerate prolonged anesthesia. Residual effects of anesthesia can delay recovery from the surgical procedure, as seen by the infant's diminished respiratory effort and apnea. For these reasons it remains unwise to extubate the infant in the immediate postoperative period. At least 24 hours of postoperative ventilation enables more control of the infant's condition and stability as well as enabling adequate postoperative pain management.

An alternate to general anesthesia is using regional anesthesia, which can be effective with less requirement for drugs; this may be beneficial in neonates with an immature physiology and metabolism. By reducing anesthetic drugs, a more stable hemodynamic response as well as faster recovery may contribute to a shortened length of stay (McCann & Soriano, 2014; Wadhwa, Hasija, & Saxena, 2017). However, close observation and assessment of pain is required for the management of postoperative pain.

Andropoulous et al. (2014) describe an association between perioperative anesthetic exposure, MRI brain injury, and neurodevelopmental outcome scores using the Bayley-III at the age of 12 months in neonates who underwent cardiac surgery. These researchers believe the recovery from brain injury can be influenced by the clinical environment, care, and length of stay in the ICU.

Stress Response

Early studies have shown that inadequate analgesia during surgery is associated with a large stress response that results in suboptimal postoperative recovery (Anand, Hansen, & Hickey, 1990). Despite this knowledge, neonates undergoing surgery continue to demonstrate a stress response, and different approaches to anesthesia and analgesia are being considered (Wolf, 2012). Surgical stress occurs as a result of an insult to the specific organ(s), tissue damage, and nociceptive stimulation presenting as an endocrine and metabolic response. The magnitude of the response is high in neonates due to the immature control of hormone secretion. The effects of the response manifest as hyperglycemia, lactic academia, tachycardia, hypertension, and hypothermia. These changes continue into the postoperative period for several hours and can obscure other clinical signs.

Thermoregulation

Concerns regarding temperature regulation continue during the intraoperative period. Although achieving a normal core temperature in the infant before surgery is always helpful, it is not always possible. Body temperature should be monitored throughout the procedure using either a skin or a rectal probe. A radiant warmer should be used during line placement, preparation, draping, and induction of anesthesia. A warming blanket under the infant can also be used to achieve constant temperature control. In addition, the room temperature should be increased to help compensate for the neonate's inability to stabilize temperature. Another mechanism for improving temperature control is humidification and warming of anesthetic gases. Slightly warming blood products, irrigation fluids, and intravenous fluids also assists in temperature maintenance. Surgical drapes should be replaced, if possible, when they become wet.

Another challenge in temperature maintenance is encountered during transport of the neonate to and from the OR. To ensure temperature stability, the infant should be covered with warmed linen during transport. During the operative procedure, the transfer bed should be warmed to allow for some warmth during transport postoperatively.

Fluid and Electrolyte Balance

The goal of intraoperative fluid management is to replace the fasting fluid deficit, maintenance and third space fluid losses, and blood loss to maintain homeostasis. Constant monitoring of fluid balance should continue throughout the surgical procedure. During the operative procedure, the fluid choice reflects the most dominant fluid loss. Early treatment of hypovolemia is essential. Intravenous fluid administration rates must be monitored to prevent fluid boluses, which could compromise fluid and electrolyte balance. Fluid loss from the surgical defect and blood loss during the operative procedure must be monitored and replaced. The metabolic response to surgery and the neuroendocrine stress response results in a rapid increase in antidiuretic hormone (ADH), which results in possible hyponatremia if the fluid sodium is not appropriate. If intraoperative free water administration is excessive, a postoperative reduction in plasma sodium ($\geq$4 mmol L) with a risk of clinically relevant postoperative hyponatremia is observed (Nkilly et al., 2014).

Monitoring

The trends of the infant's vital signs of heart rate, oxygenation, and gases are useful indicators for the anesthetist. Continuous monitoring during the operative phase can be useful in reviewing the infant's course during the surgery.

POSTOPERATIVE CARE

Oxygenation and Ventilation

Respiratory care in the postoperative period can present a great challenge to the caregiver. Intubation, anesthetic gases, and the stress of the procedure can traumatize the infant's respiratory tract. Depression of respiratory drive may be seen as a residual effect of anesthesia, and airway clearance may be difficult to maintain. These alterations in respiratory mechanics may lead to respiratory insufficiency and the need for prolonged mechanical support. Although specific respiratory needs may vary depending on the surgical procedure, a conservative approach to respiratory care is essential to maintain optimum oxygenation. Different ventilation modalities, such as high-frequency oscillation (HFO), have been found to be useful when commenced early in reducing the duration of ventilation required postoperatively (Bojan, Gioanni, Mauriat, & Pouard, 2012). An aggressive plan of weaning may cause recurring acidosis, hypoxia, or damage to the surgical repair. Following cardiac surgery, infants' slow weaning may be associated with low cardiac output and respiratory compromise.

Postoperative care of neonates includes maintaining ventilation and ensuring adequate analgesia. Small, premature, or low birth weight infants have lung function that is already compromised. The stress of severe infection and the surgical procedure itself, as well as the prematurity of the lungs, may necessitate prolonged ventilation with a slow weaning process. However, the majority of infants who undergo surgery for a congenital malformation have relatively normal lungs, and the ventilation can be quickly weaned while maintaining close observation on their work of breathing.

Pain Management

The assessment of the infant for postoperative pain is an important component of nursing care. Opioids remain the choice for pain management following major neonatal surgery. Morphine,

in particular, has proved effective and has widespread use despite its well-recognized limitation of a prolonged duration of action in neonates. Fentanyl is being used more often during neonatal surgery and for postoperative pain management, and the greater hemodynamic stability needs to be balanced against recognized disadvantages such as the early onset of tolerance (De Lima & Carmo, 2010).

Nurses need to have a good knowledge base for the physiologic responses, pharmacokinetics, and behavioral responses of the infant in pain. The use of a validated pain assessment tool and the reliability of the use of the tool between clinicians are important if postoperative pain is to be adequately managed. Most infants will have a narcotic infusion in the immediate postoperative period. The use of narcotics is encouraged; however, the assessment of their effect is important. Ceelie et al. (2012) found that despite having a protocol for postoperative pain management, it was poorly used, which can result in pain medications being underutilized. There remains a lack of information on the effectiveness of pain management strategies and outcomes of infants managed for pain with narcotics. The neonate's behavioral response and developmental capabilities are important components of the nurse's assessment. Research into the impact of the caregiving environment has revealed significant physiologic and behavioral responses to obviously painful and stressful procedures (Browne, 2011).

Fluid and Electrolyte Balance

A goal of postoperative care is to provide fluid and electrolyte balance without overhydration. Hypovolemia is a major cause of hypotension and must be resolved quickly to ensure adequate perfusion to all organ systems and to combat acidosis. However, extreme care must be taken in administering fluids because neonates are susceptible to third spacing and edema. Neonates are also very easily overloaded with excessive fluids.

Vital signs should be monitored frequently, as changes in heart rate or blood pressure could indicate shock or undetected fluid loss for which the body is trying to compensate. Assessment of temperature continues to be an important factor and must be considered when evaluating fluid needs. The serum electrolyte and glucose levels are evaluated immediately postoperatively and then intermittently until the infant's condition is stable. The frequency of laboratory evaluation is individualized to the neonate's condition. Sodium losses may continue through wound drainage as well as through gastric decompression. Thus, reevaluation of intravenous fluids, both maintenance and replacement, is required to achieve and maintain electrolyte balance. Glucose metabolism may be altered as a response to surgery. Serum glucose levels should be monitored regularly after surgery.

Replacement fluid therapy is designed to make up for abnormal fluid and electrolyte losses during therapy to reduce vomiting and for losses incurred through diarrhea, nasogastric tube drainage, stoma output, wound drainage, pleural fluid, and fistula losses. Because the constituents of these losses frequently are quite different from the composition of maintenance fluids, it may be hazardous to simply increase the volume of maintenance fluids in an attempt to compensate for these losses. In some cases, it is preferable to actually measure and analyze the electrolyte content of these losses and replace them milliequivalent for milliequivalent and milliliter for milliliter. Samples may be sent to the laboratory as needed for exact determination of the electrolyte content of these various body fluids.

Overzealous attempts to correct glucose or electrolyte problems can produce a rebound effect. The neonate may change from being hyperglycemic to being hypoglycemic without intervention over a period of minutes or hours. The neonate moves from a catabolic to an anabolic state fairly rapidly compared with an older child or adult. These phases may occur over a few days or weeks in the infant. Therefore, it is best to obtain baseline serum electrolyte and glucose levels. These values should be obtained every 2 to 4 hours, depending on how extreme the levels are. When intervention is needed, the sodium, potassium, or other electrolyte should be increased or decreased slowly and in small increments. These incremental changes should be followed by repeated measurement of serum levels, which must be closely monitored.

Nutrition

The nutritional needs of infants with altered function of the gastrointestinal tract present unique problems. Enteral feeds may be unable to be commenced, and nutrition is supplied with PN. The use of PN with increased protein is associated with beneficial outcomes, such as improved wound healing and shorter time to hospital discharge (Escobar & Caty, 2016). Neonates who undergo a stress response from abdominal surgery are able to achieve a positive protein balance with adequate support. When used, PN needs to be limited with the establishment of enteral feeds to avoid complications of PN-associated liver disease.

Feeding is usually initiated as soon as possible after surgery. This is largely controlled by the type of surgery performed and the responsiveness of the individual infant. Small trophic feeds of breast milk given every 3 to 4 hours can assist in the earlier feeding of many neonates who have undergone surgery. Infants who have undergone surgery on the gastrointestinal tract may take several days or indeed weeks before full enteral feeds are tolerated. A small stomach size with altered emptying ability, as is sometimes seen with a diaphragmatic hernia, gastroschisis, omphalocele, and bowel resection, may present paramount problems in providing proper nutrition when feedings are started. Use of continuous feedings may help with these problems. Feed tolerance is monitored with aspirations every 4 hours, with the larger volumes being returned to avoid electrolyte imbalance occurring. The routine administration of excess calories may not be warranted in critically ill surgical neonates as they do not have an increase in their resting energy expenditure. The energy is redirected from what is normally used for growth to fuel the stress response. Diligent nursing care with attention to the infant's thermal environment and supportive positioning and handling can support the infant until the infant returns to normal homeostasis following surgery.

It is imperative that the mother understands that breast milk is the first choice and that she is involved in decisions regarding feeding. When her infant returns from the surgery, her presence and an open dialogue can facilitate her ability to express and store her milk in readiness for breastfeeding as soon as possible.

Wound Care

The neonate's susceptibility to infection following surgery is due to immune suppression as a result of the trauma of surgery. This is due to changes in the neuroendocrine balance, inflammatory mediators, and both cellular and humoral components of the immune systems (Wolf, 2012). To prevent infection, nurses must provide careful handwashing and attention to wound care. Wound infections can occur during or after the surgical procedure, are related to the duration of the procedure, and can become a complicating factor. Infection occurs more often after "contaminated" surgeries, such as an intestinal perforation, compared with "clean" surgeries, such as ductal ligation. These wound infections may require treatment with antibiotics.

Nursing assessment of the site must be continual because these observations may provide the first indication of poor healing or

wound infection. The neonatal or surgical team (or both) should be made aware of any changes. If any suspicion of infection exists, blood cultures should be taken before treatment is started with broad-spectrum antibiotics that target anaerobes, aerobes, and gram-positive and gram-negative organisms. Consideration should be given to pain relief during potentially painful removal of surgical and wound dressings. The use of oral sucrose for pain relief is recommended if given 2 minutes prior to the procedure. The small volume given is not contraindicated when the infant is ordered nothing by gastrointestinal tract. New approaches to surgical incisions are being considered to give a more cosmetic effect for later in life. Comparison of different types of incisions has found no difference in terms of their postoperative outcome (Suri & Langer, 2011).

OUTCOMES

Outcomes of neonatal surgery can be considered both in the short term and in the long term. Short-term outcomes focus on issues such as recovery and establishment of feeds to enable discharge home.

Long-term consequences of neonatal surgery, if often related to the specific condition and gestational age of the neonate and early exposure to noxious or stressful stimuli such as surgery, may induce long-lasting pain behavior changes into adulthood (Escobar & Caty, 2016).

Research has shown that infants who underwent complex surgery in the newborn period to correct life-threatening birth defects performed significantly below population norms on a standardized test of infant development and were at risk of abnormal development (Laing, Walker, Ungerer, Badawi, & Spence, 2011). This finding is concerning. Laing et al. (2011) recommend that all infants undergoing major newborn surgery be routinely enrolled in systematic multidisciplinary developmental follow-up. This recommendation is supported by other specialist groups (Liddell, Walker, & Davis, 2011) that recommend long-term follow-up for all survivors of congenital diaphragmatic hernia surgery. This long-term follow-up care is critical to identify and proactively manage comorbidities.

Neurodevelopmental outcomes in school-age children were found to be reduced in children who underwent an arterial switch operation; however, there was no cognitive dysfunction. Cognitive and motor developmental delay was found in 23% of children who had surgery in the newborn period for noncardiac conditions (Stolwijk et al., 2016). Infant temperament following surgery for complex congenital heart disease was found to be a significant source of stress for the parents (Torowicz, Irving, Hanlon, Sumpter, & Medoff-Cooper, 2010), and predischarge guidance for the families is recommended. These outcomes need to be considered when following infants who have undergone neonatal surgery. Major neurosensory disability was found to be higher at 8 years of follow-up in extremely preterm infants who underwent surgery during their initial hospital admission (Hunt et al., 2018). These rates of disability have not changed over time and may indicate a need to examine the caregiving and management of surgical preterm infants in the NICU. It appears that the experience of surgery, neonatal intensive care, and hospitalization can be deleterious for sick infants and their families. Care needs to be taken to ensure that the stressors encountered are kept to a minimum, and nurses are in key positions to provide a quality focus to the care of these infants and families.

Socioeconomic and psychosocial factors are also important contributors to variability in longer term outcomes for infants and families and indicate a link between parent factors and child developmental outcomes following newborn surgery for birth defects (Laing et al., 2011). Further research is needed to identify how best to incorporate nursing practices that enable caregivers to simultaneously meet the medical and developmental needs of vulnerable infants and promote positive parent–child interactions in a surgical neonatal context. Evaluating the appropriateness of such care practices may require a multimodal approach and may also be developmentally directed, family-centered, and humane care judged by common sense (Laing, Spence, McMahon, Ungerer, & Badawi, 2012).

Data on many specific congenital malformations requiring neonatal surgery are now being collected through specific registries, both national and international. These registries enable a more population-based measurement of outcomes and provide an opportunity for earlier and newer treatments to be considered.

SUMMARY

This chapter highlights the special considerations for the neonate undergoing surgery and his or her family. These vulnerable infants require vigilance during their pre-, intra-, and postoperative course. The role of care coordination and fluid, electrolyte, and nutrition management are essential elements of this care. Follow-up programs enable the treatments to be evaluated and the effects of anesthetics to be monitored.

CASE STUDY

An infant born at 30 weeks' gestation who is now 2 weeks of age was transferred to a regional surgical center due to increasing abdominal distention and feed intolerance.

The transport team reported some instability prior to transport with unstable temperature and increasing respiratory effort requiring intubation for respiratory support during transfer.

Once in the surgical neonatal intensive care unit, the infant was stabilized. On initial assessment the temperature was 36.8°C, color pale with some webbing on chest, increased work of breathing above the ventilator rate of 40 breaths/minute, and a heart rate of 160 beats/minute. When attached to the monitor, the saturation was 98%.

An abdominal x-ray showed distended loops of small bowel with some pneumatosis. Fluid levels were seen on the lateral view. The neonatal team and surgical team consulted and agreed to plan exploratory surgery.

Prior to transfer to the OR, the neonatal nurse attended to the following:

- Warming the infant to a normal temperature of 37.5°C by placing in an incubator within the infant's neutral thermal range
- Administering pain relief with a morphine infusion following assessment through a pain score
- Positioning the infant in a supported flexed position to avoid undue strain in the distended abdomen
- Placing an 8 FR gastric tube to ensure the stomach is vented and avoiding risk of aspiration
- Assessing the respiratory support to maintain adequate acid–base balance, oxygenation, and perfusion
- Reassuring the parents and supporting them to hold their baby during transfer to the transport bed

In preparation for transfer to the OR, the following were checked and attended:

- A warmed transport cot was prepared with portable oxygen and air and the transport ventilator settings appropriate for the infant.
- Consent form signed by parents after explanation from surgeon.

- Infant's head and limbs wrapped in cotton webbing for added warmth ensuring abdomen is free for surgeon.
- IV cannula patent and secured and pump and fluid settings correct.
- All documentation correct and available for the staff in the OR.
- Identification bands placed on infant's limbs after checking information is correct.

During transfer from the SNIC to the OR, the nurse attended to the following:

- Closely observed the infant to signs of stress or deterioration
- Had the parents accompany their baby to the OR door with a chance to say good-bye
- Handed over to the staff in the OR ensuring they had a good understanding of the infant's history, gestational age, and need for warmth and fluid control
- Ensured the transfer bed was plugged in to maintain warmth for the postoperative transfer

This case demonstrates the need for a team approach and the importance of assessment and preparation of the infant for surgery. Attention to small details can ensure the transfer process is smooth with no delays or emergency situations.

CASE STUDY

During the operation, attention needs to be paid to fluid administration, warmth, and adequate pain relief during the procedure. This is the role of the anesthetist. However, as a neonatal nurse caring for the infant following surgery, it is important to be aware of the infant's management during the operation. Reviewing the intraoperative records can assist in gathering this information.

Critically review the following article in terms of different neonates who require surgery:

1. 30 weeks' gestation with necrotizing enterocolitis (NEC)
2. Infant who weighs 800 g requiring a patent ductus arteriosus (PDA) ligation
3. Term infant with cardiac abnormality
4. 36 weeks' gestation infant with a gastroschisis

Reference

Vadi, M., Nour, C., Leiter, P., & Carter, H. (2017, May 3). Anesthetic management of the newborn surgical patient. In J. Baerg (Ed.), *Pediatric and neonatal surgery*. London, England: IntechOpen. doi:10.5772/66932

EVIDENCE-BASED PRACTICE BOX

Measuring neurodevelopmental outcomes has become an important component in the continuum of neonatal surgery. There are many studies now examining the effects of anesthesia, drugs, and prolonged stay in the NICU. As more infants survive, the neurodevelopmental outcomes become a focus on care and future resources.

The anesthetic and the volatile drugs used can be harmful. Andropoulos et al. (2014) demonstrated an association between perioperative anesthetic exposure, MRI brain injury, and neurodevelopmental outcome scores using the Bayley-III at the age of 12 months. Larger anesthetic exposure and new postoperative brain injury on MRI were associated with lower neurodevelopmental scores. They state that the duration of ICU stay, with or without brain injury, was most strongly associated with poor neurocognitive outcome assessed with a 12-month Bayley-III.

The effects of neonatal surgery on preterm infants have also been studied. Filan et al. (2012) found that preterm infants exposed to surgery and anesthesia had greater white matter injury and smaller total brain volumes. They recommend that surgical exposure in the preterm infant should alert the clinician to an increased risk for adverse cognitive outcome. Hunt et al. (2018) found there was a greater neurosensory disability at 8 years of very preterm infants who underwent neonatal surgery.

Birth during the early term period of 37 to 38 weeks' gestation is associated with worse outcomes following neonatal cardiac surgery (Costello et al., 2014). Gaynor et al. (2015) found that neurodevelopmental outcomes after cardiac surgery in newborns are below population means and have not improved in recent years. Cognitive and motor developmental delay was found in 23% of patients with noncardiac conditions who required neonatal surgery (Stolwijk et al., 2016).

References

Andropoulos, D. B., Ahmad, H. B., Haq, T., Brady, K., Stayer, S. A., Meador, M. R., . . . Easley, R. B. (2014). The association between brain injury, perioperative anesthetic exposure, and 12-month neurodevelopmental outcomes after neonatal cardiac surgery: A retrospective cohort study. *Pediatric Anesthesia, 24*(3), 266–274. doi:10.1111/pan.12350

Costello, J. M., Pasquali, S. K., Jacobs, J. P., He, X., Hill, K. D., Cooper, D. S., . . . Jacobs, M. L. (2014). Gestational age at birth and outcomes after neonatal cardiac surgery: An analysis of the Society of Thoracic Surgeons (STS) Congenital Heart Surgery Database. *Circulation, 129*(24), 2511–2517. doi:10.1161/CIRCULATIONAHA.113.005864

Filan, P. M., Hunt, R. W., Anderson, P. J., Doyle, L. W., & Inder, T. E. (2012). Neurologic outcomes in very preterm infants undergoing surgery. *The Journal of Pediatrics, 160*(3), 409–414. doi:10.1016/j.jpeds.2011.09.009

Hunt, R. W., Hickey, L. M., Burnett, A. C., Anderson, P. J., Cheong, J. L. Y., & Doyle, L. W. (2018). Early surgery and neurodevelopmental outcomes of children born extremely preterm. *Archives of Disease in Childhood—Fetal and Neonatal Edition, 103*(3), F227–F232. doi:10.1136/Archdischild-2017-313161

Gaynor, W., Stopp, C., Wypij, D. B., Andropoulos, D. B., Atallah, J., Atz, A. M., . . . Newburger, J. W. (2015). Neurodevelopmental outcomes after cardiac surgery in infancy. *Pediatrics, 135*, 816–825. doi:10.1542/peds.2014-3825

Stolwijk, L. J., Lemmers, P. M., Harmsen, M., Groenendaal, F., de Vries, L. S., van der Zee, D. C., . . . van Herwaarden-Lindeboom, M. Y. (2016). Neurodevelopmental outcomes after neonatal surgery for major noncardiac anomalies. *Pediatrics, 137*(2), e20151728. doi:10.1542/peds.2015-1728

ONLINE RESOURCES

Deshmukh, A. (2013). *Surgical emergencies in newborn* [Slide presentation]. Retrieved from https://www.slideshare.net/abhilesh07/surgical-emergencies-in-newborn

Esophageal atresia-Treatment-Pediatirc Playbook. Retrieved from https://www.youtube.com/watch?v=ktIEsQ8_CEo

Neonatal surgery: An overview. Retrieved from https://www.sciencedirect.com/topics/medicine-and-dentistry/neonatal-surgery

Spence, R. K., & Wait, R. B. (Eds.). (1998). *Frequently encountered problems in neonatal surgery.* Retrieved from https://medicine.stonybrookmedicine.edu/system/files/scriven-1.pdf

Surgical Neonates. (2004). Newborn services clinical guideline. Retrieved from http://www.adhb.govt.nz/newborn/Guidelines/Surgery/SurgicalNeonates.htm

UCSFPediatricSurgery. (2012). *Gastroschisis—Your operation* [Video file]. Retrieved from https://www.youtube.com/watch?v=Zo3cZH_7BRs

Yutchawit, P. (2014). Congenital diaphragmatic hernia [Slide presentation]. Retrieved from https://www.slideshare.net/FTmed38/topic-cdh"?

REFERENCES

Andropoulos, D. B., Ahmad, H. B., Haq, T., Brady, K., Stayer, S. A., Meador, M. R., . . . Easley, R. B. (2014). The association between brain injury, perioperative anesthetic exposure, and 12-month neurodevelopmental outcomes after neonatal cardiac surgery: A retrospective cohort study. *Paediatric Anaesthesia, 24*(3), 266–274. doi:10.1111/pan.12350

Anand, K. J. S., Hansen, D. D., & Hickey, P. R. (1990). Hormonal–metabolic stress responses in neonates undergoing cardiac surgery. *Anesthesiology, 73(4)*, 661–670. doi:10.1097/00000542-199010000-00012

Badawi, N., Adelson, P., Roberts, C., Spence, K., Laing, S., & Cass, D. (2003). Neonatal surgery in New South Wales—What is performed where? *Journal of Pediatric Surgery, 38*(7), 1025–1031. doi:10.1016/S0022-3468(03)00184-2

Bojan, M., Gioanni, S., Mauriat, P., & Pouard, P. (2012). High-frequency oscillatory ventilation and short-term outcome in neonates and infants undergoing cardiac surgery: A propensity score analysis. *Critical Care, 15*(5), R259. doi:10.1186/cc10521

Browne, J. V. (2011). Developmental care for high-risk newborns: Emerging science, clinical application, and continuity from newborn intensive care unit to community. *Clinical Perinatology, 38*(4), 719–729. doi:10.1016/j.clp.2011.08.003

Calisti, A., Oriolo, L., Giannino, G., Spagnoi, L., Molle, P., Buffone, E., & Donadio, C. (2012). Delivery in a tertiary center with co-located surgical facilities makes the difference among neonates with prenatally diagnosed major abnormalities. *Journal of Maternal Fetal Neonatal Medicine, 25*(9), 1735–1737. doi:10.3109/14767058.2012.663819

Cass, D. L. (2011). Impact of prenatal diagnosis and therapy on neonatal surgery. *Seminars in Fetal and Neonatal Medicine, 16*(3), 130–138. doi:10.1016/j.siny.2011.03.007

Ceelie, I., de Wildt, S. N., de Jong, M., Ista, E., Tibboel, D., & van Dijk, M. (2012). Protocolized post-operative pain management in infants; do we stick to it? *European Journal of Pain, 16*(5), 760–766. doi:10.1002/j.1532-2149.2011.00056.x

Davidson, A. J., & Sun, L. S. (2018). Clinical evidence for any effect of anesthesia on the developing brain. *Anesthesiology, 128*(4), 840–853. doi:10.1097/ALN.0000000000001972

De Lima, J., & Carmo, K. B. (2010). Practical pain management in the neonate. *Best Practice and Research Clinical Anaesthesiology, 24*(3), 291–307. doi:10.1016/j.bpa.2010.04.001

Diffin, J., Spence, K., Johnston, L., & Badawi, N. (2012). Predictors of psychological distress in mothers and fathers of neonates admitted to the neonatal intensive care unit for surgical correction of a congenital anomaly. *Journal of Paediatrics and Child Health, 48*(Suppl. 1), 8–81. doi:10.1111/j.1440-1754.2012.02411.x

Escobar, Jr, M. A., & Caty, M. G. (2016). Complications in neonatal surgery. *Seminars in Pediatric Surgery, 25*(6), 347–370. doi:10.1053/j.sempedsurg.2016.10.005

Fullerton, B. S., Sparks, E. A., Morrow, K. A., Edwards, E. M., Soll, R. F., Jaksic, T., … Modi, B. P. (2016). Hospital transfers and patterns of mortality in very low birth weight neonates with surgical necrotizing enterocolitis. *Journal of Pediatric Surgery, 51*(6), 932–935. doi:10.1016/j.jpedsurg.2016.02.051

Gallagher, K. (2013). Neonatal nursing education provision in the United Kingdom. *Journal of Neonatal Nursing, 19*(5), 224–232. doi:10.1016/j.jnn.2013.04.013

Hunt, R. W., Hickey, L. M., Burnett, A. C., Anderson, P. J., Yoong Cheong, J. L., & Doyle, L. W. (2018). Early surgery and neurodevelopmental outcomes of children born extremely preterm, *Archives of Disease in Childhood—Fetal and Neonatal Edition, 103*(3), F227–F232. doi:10.1136/Archdischild-2017-313161

Laing, S., Spence, K., McMahon, C., Ungerer, J., & Badawi, N. (2012). Challenges in conducting prospective research of developmentally directed care in surgical neonates: A case study. *Early Human Development, 88*(3), 171–178. doi:10.1016/j.earlhumdev.2011.08.003

Laing, S., Walker, K., Ungerer, J., Badawi, N., & Spence, K. (2011). Early development of children with major birth defects requiring newborn surgery. *Journal of Paediatrics and Child Health, 47*(3), 140–147. doi:10.1111/j.1440-1754.2010.01902.x

Lakhoo, K. (2012). Fetal counselling for surgical conditions. *Early Human Development, 88*(1), 9–13. doi:10.1016/j.earlhumdev.2011.11.004

Liddell, M., Walker, G., & Davis, C. (2011). Modern management of congenital diaphragmatic hernia. *Infant, 7*(3), 92–97. Retrieved from http://www.infantjournal.co.uk/pdf/inf_039_tic.pdf

McAteer, J. P., LaRiviere, C. A., Drugas, G. T., Abdullah, F., Oldham, K. T., & Goldin, A. B. (2013). Influence of surgeon experience, hospital volume, and specialty designation on outcomes in pediatric surgery: A systematic review. *Journal of the American Medical Association Pediatrics, 167*(5), 468–475. doi:10.1001/jamapediatrics.2013.25

McCann, M. E., & Soriano, S. G. (2014). Progress in anesthesia and management of the newborn surgical patient. *Seminars in Pediatric Surgery, 23*(5), 244–248. doi:10.1053/j.sempedsurg.2014.09.003

McFadyen, B., Harms, L., Johnston, L., Anderson, P., Badawi, N., Evans, C., . . . Spence, K. (2011). Exploring the impact of family care-giving following neonatal surgery: Caring for infants with surgically correctable congenital anomalies of the abdomen and airways. *Journal of Paediatrics and Child Health, 47*(Suppl. 1), 60–116. doi:10.1111/j.1440-1754.2011.02047.x

McKean, E. B., Kasparian, N. A., Batra, S., Sholler, G. F., Winlaw, D. S., & Dalby-Payne, J. (2017). Feeding difficulties in neonates following cardiac surgery: Determinants of prolonged feeding-tube use. *Cardiology in the Young, 27*(6), 1203–1211. doi:10.1017/S1047951116002845

Mehta, B., Hunt, R., Walker, K., & Badawi, N. (2016). Evaluation of preoperative amplitude-integrated electroencephalography (aEEG) monitoring for predicting long-term neurodevelopmental outcome among infants undergoing major surgery in the neonatal period. *Journal of Child Neurology. 31*(11), 1276–1281. doi:10.1177/0883073816653781

Neunhoeffer, F., Warmann, S. W., Hofbeck, M., Müller, A., Fideler, F., Seitz, G., . . . Fuchs, J. (2017). Elevated intrathoracic CO_2 pressure during thoracoscopic surgery decreases regional cerebral oxygen saturation in neonates and infants—A pilot study. *Paediatric Anaesthesia, 27*(7), 752–759. doi:10.1111/pan.13161

Nkilly, E., Michelet, D., Hilly, J., Diallo, T., Greff, B., Mangalsuren, N., . . . Dahmani, S. (2014). Postoperative decrease in plasma sodium concentration after infusion of hypotonic intravenous solutions in neonatal surgery. *British Journal of Anaesthesia, 112*(3), 540–545. doi:10.1093/bja/aet374

Stolwijk, L. J., Lemmers, P. M., Harmsen, M., Groenendaal, F., de Vries, L. S., van der Zee, D. C., . . . van Herwaarden-Lindeboom, M. Y. A. (2016). Neurodevelopmental outcomes after neonatal surgery

for major noncardiac anomalies. *Pediatrics, 137*(2), e20151728. doi:10.1542/peds.2015-1728

Suri, M., & Langer, J. C. (2011). A comparison of circumumbilical and transverse abdominal incisions for neonatal abdominal surgery. *Journal of Pediatric Surgery, 46(6)*, 1076–1080. doi:10.1016/j.jpedsurg.2011.03.032

Taneja, B., Srivastava, V., & Saxena, K. N. (2012). Physiological and anaesthetic considerations for the preterm neonate undergoing surgery. *Journal of Neonatal Surgery, 1*(1), 14.

Tauro, J. K., Walker, K., Halliday, R., Jatana, V., & Trivdi, A. (2018). Trends in mortality in an Australian tertiary surgical neonatal intensive care unit, *Journal of Neonatal Surgery, 7*(1), 4. doi:10.21699/jns.v7i1.677

Torowicz, D., Irving, S. Y., Hanlon, A. L., Sumpter, D. F., & Medoff-Cooper, B. (2010). Infant temperament and parental stress in 3 month old infants following surgery for congenital heart disease. *Journal of Developmental and Behavioral Pediatrics, 31*(3), 202–208. doi:10.1097/DBP.0b013e3181d3deaa

Usui, N., Kamiyama, M., Tani, G., Kanagawa, T., & Fukuzawa, M. (2011). Use of the medical information on the Internet by pregnant patients with a prenatal diagnosis of neonatal disease requiring surgery. *Pediatric Surgery International, 27*(12), 1289–1293. doi:10.1007/s00383-011-2965-6

Vadi, M., Nour, C., Leiter, P., & Carter H. (2017, May 3). Anesthetic management of the newborn surgical patient, In J. Baerg (Ed.), *Pediatric and neonatal surgery*. London, England: IntechOpen. doi:10.5772/66932

Wadhwa, B., Hasija, N., & Saxena, K. N. (2017). Regional anaesthesia for the neonate. *Journal of Neonatal Surgery, 6*(4), 79–83. doi:10.21699/jns.v6i4.665

Wilpers, A. B., Kennedy, H. P., Wall, D., Funk, M., & Bahtiyar, M. O. (2017). Maternal anxiety related to prenatal diagnoses of fetal anomalies that require surgery. *Journal of Obstetric, Gynecologic and Neonatal Nursing, 46*(3), 456–464. doi:10.1016/j.jogn.2017.02.001

Wolf, A. (2012). Effects of regional analgesia on stress responses to pediatric surgery. *Pediatric Anesthesia, 22*(1), 19–24. doi:10.1111/j.1460-9592.2011.03714.x

CHAPTER 26

Emerging Infections

Kathryn R. McLean and Tami Wallace

INTRODUCTION

Emerging infections are those infectious agents whose incidence has increased within the past two decades or have the potential to increase in the near future. It includes zoonotic pathogens that have crossed over from an animal population, organisms that develop resistance to antimicrobials, new mutations, seldom-occurring pathogens recognized through new detection methods, and re-emergence of organisms that had been controlled in the past but are making a comeback (Greenfield & Bronze, 2010; Stramer et al., 2009). Scientists estimate that more than three new human pathogen species have been discovered each year since 1980 (Morgan, Kirkbride, Hewitt, Said, & Walsh, 2009). While not all of these pathogens have entered the NICU, they all have the potential. A list of emerging infections is provided in Table 26.1.

As we discuss these pathogens, it becomes evident that this is very much a global problem. The Zika virus range expanded from first identification in Africa to scattered outbreaks in French Polynesia, to a pandemic involving citizens of 84 countries (McArthur, 2017; Rawal, Yadav, & Kumar, 2016). Methicillin-resistant *Staphylococcus aureus* (MRSA) has been reported in NICUs throughout the world (Chuang et al., 2004; Huang, Lien, Su, Chou, & Lin, 2011; Lepelletier et al., 2009; Nambiar, Herwaldt, & Singh, 2003; Regev-Yochay et al., 2005; Sakamoto, Yamada, Suzuki, Sugiura, & Tokuda, 2010; Seybold et al., 2008; Shirai et al., 2017; H. A. Silva et al., 2009). Air travel allows transmission between hosts on different continents in a matter of hours. It is possible to travel between most countries in less time than the incubation period for many infectious diseases (Castillo-Salgado, 2010). The expanding human population and loss of animal habitats bring closer proximity to wildlife, reservoirs of zoonotic pathogens that can emerge in humans (Brouqui, 2009; Wendelboe, Grafe, & Carabin, 2010). Climate changes can allow range expansion of arthropods and rodents, vectors of viruses such as the Zika virus and tick-borne protozoa such as *Babesia microti* (Gould, 2009; Rather, Lone, Bajpai, Paek, & Lim, 2017).

As we study emerging infections, we see a pattern of response consisting of four stages. This chapter describes these stages, using the Zika virus to illustrate the pattern. This pattern of response offers a framework to deal with future emerging infections.

It is important for the NICU team to understand how resistance develops and what steps can be taken to minimize the development of resistant organisms. Knowledge of chromosomal genetics and antimicrobial pharmacodynamics assists in this understanding. Infection control and antimicrobial stewardship are key elements to reduce the impact of resistance.

MATERNAL, FETAL, AND NEONATAL SUSCEPTIBILITY TO INFECTIOUS DISEASES

Outcomes for mothers and their infants are intertwined and interdependent. Pregnant women have increased susceptibility and increased severity of some types of infections during pregnancy. During pregnancy women are more susceptible to some infections such as listeriosis and HIV, but these disorders are not necessarily more severe during pregnancy. Other infections such as influenza and herpes simplex are no more likely to occur during pregnancy, but are more severe in pregnancy and may affect the newborn (Kourtis, Read, & Jamieson, 2014). Current medical science cannot yet fully explain all the reasons for the specific changes seen in pregnancy, but it is believed that a number of factors contribute to these alterations. Alterations in the immune system to allow tolerance of the fetal allograft, the effects of hormones on immune function, and the mechanical changes due to the enlarging fetus affect the pregnant woman's ability to fight infections (Kourtis et al., 2014). Infections in the mother can affect the fetus. Even when the fetus is protected from active infection, there may be teratogenic effects from maternal, placental, and fetal inflammatory cytokines (Kourtis et al., 2014).

The neonatal immune system is discussed more completely in Chapter 11, Immune System, but it is important to remember the limitations of the neonatal immune response when discussing emerging infections. The neonate has limitations in both the innate and the adaptive immune systems, making them particularly at risk for new and novel pathogens (Simon, Hollander, & McMichael, 2015). This intertwining of maternal and neonatal outcomes was evident in the 2009 pandemic with the H1N1 influenza virus. In the United States, it was recognized quite early that pregnant women were more likely than the general population to require hospitalization (Jamieson et al., 2009). Colleagues in the United Kingdom published data to demonstrate increased mortality and morbidity born to women infected with H1N1 (Pierce, Kurinczuk, Spark, Brocklehurst, & Knight, 2011). By mid-2011, there were enough data from multiple countries to publish a systematic review of literature with numbers of cases in pregnancy, additional risk factors, maternal outcomes, and neonatal outcomes (Mosby, Rasmussen, & Jamieson, 2011).

TABLE 26.1

EMERGING AND RE-EMERGING INFECTIONS IN NEONATES

Infection	Agent	Diagnosis	Spread	Consequences/ Treatment	Comments
Zika	Zika virus	Travel history + PCR or ELISA at the CDC-approved laboratories	Mother to fetus	Fetus: Brain defects in fetus, miscarriage and stillbirth No specific treatment	
Chagas	*Trypanosoma cruzi* parasite	Parasite on blood smear or PCR (antibody testing not helpful in newborn period)	Triatomine insect bite Or transfer from mother to fetus	Newborn: Most have mild or no signs May have low birthweight, prematurity, hepatosplenomegaly, anemia, thrombocytopenia Treatment: Nifurtimox and benznidazole	
Syphilis	*Treponema pallidum* bacterium, spirochete	RPR or VDRL, dark-field microscopic evaluation of any secretions, PCR (antibody testing may not be helpful in newborn period)	Mother to infant	Nonimmune hydrops, jaundice, hepatosplenomegaly, rhinitis, rash, pseudoparalysis of extremity, osseous lesions Treatment: Penicillin for 10 days	Reportable in all 50 states
Hepatitis C	HCV	Cannot be tested in newborn period, HCV RNA may be seen as early as 1–2 months	Mother to infant (5%–6% if mother is HIV negative and ~14% if mother is HIV positive; Alter et al., 1998) Not documented to be passed in breast milk	None in newborn period	Many exposed infants lost to follow-up Can develop chronic disease
CMV	CMV virus	PCR on saliva and urine	Mother to fetus, in breast milk, community contacts	Wide range of presentation from asymptomatic to fulminant viremia. Low birth weight, liver problems, microcephaly, seizures, hearing loss, vision loss, intellectual disability, lack of coordination Treatment: Ganciclovir or valganciclovir	May develop hearing loss even after passing newborn screen. Need long-term follow-up
Disease X	Unknown	The WHO has put potential disease on their priority list for monitoring A reminder that a new, potential disease-causing pathogen may quickly appear			

May present special risk specifically to NICU patients:
Multidrug-resistant bacteria
Resistant fungus
Diseases that are re-emerging due to lack of vaccination (e.g., measles)

CDC, Centers for Disease Control and Prevention; CMV, cytomegalovirus; HCV, hepatitis C virus; PCR, polymerase chain reaction; RPR, rapid plasma reagin; VDRL, Venereal Disease Research Laboratory; WHO, World Health Organization.

Source: World Health Organization. (n.d.). *List of Blueprint priority diseases*. Retrieved from http://www.who.int/blueprint/priority-diseases/en

HUMAN DRIVERS OF EMERGING INFECTIONS

Humans can and do influence many of the drivers of emerging infections. Globalization, changes in population density, climate change, antibiotic use, and intentional interventions all impact the types, location, and spread of these infections.

Many authors point to globalization as an important driver of emerging infections (Beigi, 2017; Rogalski, Gowler, Shaw, Hufbauer, & Duffy, 2016; Hopkins, 2007). Modern life with its increased global travel and trade facilitates the rapid spread of diseases. We are one day and one plane ride away from distant destinations. Our food and supply sources are international. People, supplies, and diseases can travel long distances in a short period of time. Movement of humans and disease vectors can expose naive hosts to novel infections. Local systems may not be prepared to recognize, treat, or prevent the spread of what are to them novel infections. The potential consequences are significant.

The effects of globalization were demonstrated in the 2014 Ebola outbreak. Ebola is a virus that probably originated in bats, but has now moved to humans. It can cause a hemorrhagic disease and is extremely deadly. In 2014, the Ebola virus quickly moved from an outbreak in a handful of African countries to a disease with repercussions for travel and healthcare around the world. An estimated 24 cases of Ebola were treated in Europe and the United States. Many of these cases were aid workers who traveled back to their home countries for treatment (Ashkenas et al., 2015), but others were travelers who unknowingly brought the disease with them. Transmission is by contact with infected secretions. At least one Ebola victim traveled from Liberia to Texas before becoming ill. Two nurses were infected in the process of caring for him. This infection in young women of childbearing age started a discussion about the possibility of Ebola in pregnancy, in the neonate, and in the NICU. This remained just a discussion as there were no documented cases in pregnancy outside of Africa. The cases moved from country to country within days, and each case was multinational news within hours thanks to modern communications. In a very short time, an outbreak in a small part of Africa became an international concern that required international collaboration and responses. Worldwide collaboration and knowledge sharing helped contain the outbreak.

Humans drive the location, evolution, and types of infections by multiple mechanisms. Modern life, technology, and medical care have multiple consequences that are far-reaching, unintended, and possibly unanticipated. Examples of proposed mechanisms for which there is empiric support are summarized in Table 26.2.

TABLE 26.2

HUMAN DRIVERS OF EMERGING INFECTIONS: MECHANISMS AND POTENTIAL EFFECTS

Proposed Mechanism	Potential Effects
Global travel and trade	• Rapid movement of people, pathogens • Movement of disease vectors (e.g., mosquitoes, rats)
Changes in population density	• Increased density creates potential for increased spread of infection (Rogalski et al., 2016)
Climate change	• Changes in vector density, diversity, and location (Rogalski et al., 2016) • Changes in human population density
Antibiotic use and abuse	• Antibiotic resistance • Changes to the human microbiome and host response
New vectors	• Blood transfusion (Flaherty, Moran, & Higgins, 2017) and organ transplantation as a vector
Intentional interventions	• Immunization • Decreasing vector populations (e.g., spraying for mosquitoes) (Rogalski et al., 2016)
Bioterrorism	• Potential deliberate spread of infection (American Academy of Pediatrics & the American College of Obstetricians and Gynecologists, 2017)

TRENDS IN EMERGING INFECTIONS

In 2007, the World Health Organization (WHO) first warned of the increasing number of emerging infections over time and of the more rapid spread of these infections. At the time, they cited a world that was increasingly mobile and interdependent as providing opportunities for the spread of infectious disease. The WHO called for global collaboration, pointing to the need for an increased capacity for rapid reporting, sharing, and improved response to assure health security (Hopkins, 2007). Many organizations such as the WHO, the United States Centers for Disease Control and Prevention (CDC), and other ministries of health have labored to create reporting structures and response systems. The WHO created the Emergency Response Framework to guide these processes (WHO, 2013). This framework has been expanded and updated over time. Thus, critical response teams at local and international levels have been created and have helped guide efforts in recent years. A recent example is the widespread and rapid response to the Zika virus and its potential fetal affects.

PATTERN OF RESPONSE TO EMERGING INFECTIONS

One approach to looking at emerging infections is to recognize a pattern of response. The pattern of response to emerging infections consists of four stages. The first stage, *Discovery*, begins with recognition of a new infectious agent. It is often precipitated by a global health crisis. Examples of such health crises include the hemorrhagic deaths associated with the Ebola outbreak in 2014 and the increased incidence of microcephaly following Zika virus infection noted in Brazil from 2015 to 2017. Surveillance programs and epidemiology studies provide evidence of emerging infections and their association with specific health crisis. The second stage, *Definition*, involves investigation into the causative agent: what are its properties, genetic make-up, methods of

transmission, and impact on victims. The third stage, *Defense*, involves the further development of tools to quickly identify the organism, prevention of new cases, and finding treatments to lessen the impact of the infection. The third stage is time-consuming as it often involves clinical trials of pharmaceuticals. There is often overlap between the second and third stage as new studies into the properties of the organism identify weaknesses that can be exploited with different therapies. The fourth stage, *De-escalation*, recognizes that the incidence of an emerging infection often wanes over time. The fourth stage can be a result of prevention, successful therapies, or part of the natural course of the emerging infection. HIV is an example of an infection which responded to pharmacological treatment, resulting in a decrease in new cases. In the natural course of an infection, the person who contracts the infection develops immunity and no longer acts as a host. H1N1 (swine flu) is an example of the natural decline; it is no longer an emerging infection as it peaked in 2009 to 2010 (Thorner, 2018). Arrival at the fourth stage does not eliminate the potential for re-emergence should a new population be exposed or resistance to pharmacologic treatment develop.

ZIKA VIRUS

The Zika virus was discovered in a rhesus monkey in the Zika forest of Uganda during a surveillance for yellow fever in 1947 (Passi, Sharma, Dutta, & Ahmed, 2017). In 1948, it was isolated from a mosquito. The first human infections were identified in 1952 in Uganda and Tanzania. Scattered mild infections occurred in Africa and Southeast Asia. The first outbreak occurred in 2007 on the island of Yap. Also, there was a major outbreak in 2013 in French Polynesia. During this outbreak, an increase in neurologic complications occurred and 73 cases of Guillain–Barré syndrome were identified (Eppes et al., 2017; McArthur, 2017). Beginning in 2015, a major outbreak was first noted in Brazil, eventually spreading throughout South and Central America and as far north as the states of Florida and Texas in the United States. Cases have been reported in 84 countries as of March 2017 (McArthur, 2017). An increase in microcephaly associated with mothers who developed a Zika infection prompted the WHO to announce a Public Health Emergency on February 8, 2016 (Oussayef et al., 2017). This recognition of Zika virus as a potential causative agent represents stage 1 (Discovery) of the Pattern of Response to Emerging Infections.

During stage 2 (Definition), surveillance and epidemiology studies and scientific investigation supported the causative nature between Zika virus infection in mothers and a congenital Zika syndrome (CZS). All infants with CZS tested positive for the Zika virus (Acosta-Reyes et al., 2017; Mattar et al., 2017; Reagan-Steiner et al., 2017). CZS involves neurologic, musculoskeletal, ocular, and possible cardiac deformities. Zika virus infection was associated with a 20-fold increase in microcephaly (Cragan et al., 2017; Marrs et al., 2016; A. Sharma & Lal, 2017). Those infants who developed severe microcephaly (with head circumference <3 standard deviations [SDs] below the mean) had a distinct craniofacial appearance with sloping forehead, overlapping cranial bones with partial collapse of the bones of the upper skull, and redundant scalp skin folds (Adebanjo et al., 2017; A. A. M. Silva et al., 2016; van der Linden, Filho et al., 2016;). Brain abnormalities detected by CT include microcephaly (head circumference <2 SDs below the mean), decreased brain volume with malformation of cortical development (such as lissencephaly and polymicrogyria), brain calcifications primarily at the cortical–white matter junction, ventriculomegaly, hypoplasia of the cerebellum, hypoplastic or absent corpus callosum, and hypoplasia of the ventral cord (Adebanjo et al., 2017; Petribu et al., 2017). Follow-up of infants without microcephaly at birth has shown occasions where head growth decelerated to the point of microcephaly months after birth (van der Linden, Pessoa, et al., 2016). Seizures occurred in over 50% of infants (A. A. M. Silva et al., 2016). Clinical findings may include hypertonia, irritability, dysphagia, dystonia, dyskinesia, hemiparesis, arthrogryposis (presence of multiple contractures associated with decreased fetal movement), or spastic quadriplegia (van der Linden, Filho, et al., 2016; van der Linden, Pessoa, et al., 2016; Pessoa et al., 2018). Ocular abnormalities include macular scarring with focal pigmentary retinal mottling, microphthalmia, coloboma, intraocular calcifications, optic nerve hypoplasia, and atrophy (Adebanjo et al., 2017; Ventura & Ventura, 2018). There is an association with sensorineural hearing loss (Leal, Muniz, Ferreira, et al., 2016; Leal, Muniz, Caldas Neto, van der Linden, & Ramos, 1016). DiCavalcanti et al. (2017) performed echocardiography on 103 infants with CZS and found that 13.5% had congenital heart disease. These findings included atrial septal and ventricular septal defects (DiCavalcanti et al., 2017). Fetal growth restriction or fetal loss can occur (Saiz et al., 2017; van der Eljk et al., 2016). In the United States and its territories, the prevalence of congenital birth defects associated with maternal Zika infection during pregnancy is approximately 5% (Shapiro-Mendoza et al., 2017). Malformations associated with CZS are summarized in Table 26.3.

Multiple studies confirmed the role of Zika virus infection in developmental brain abnormalities. In vitro experiments involving

TABLE 26.3

MALFORMATIONS ASSOCIATED WITH CONGENITAL ZIKA SYNDROME

System	Malformation
Neurologic	Microcephaly Hydrocephaly Lissencephaly Polymicrogyria Holoprosencephaly Ventriculomegaly Absent corpus callosum Intracerebral calcifications Pachygyria Agyria
Ocular	Optic nerve abnormalities Chorioretinal atrophy Maculopathies Vasculopathies
Musculoskeletal	Craniofacial abnormalities (sloped forehead) Clubfeet Arthrogryposis Craniosynostosis Hip dysplasia
Cardiovascular	Atrial septal defect Ventricular septal defect
Miscellaneous	Intrauterine growth restriction Anasarca Pulmonary hypoplasia

Zika virus infection of human neural progenitor cells showed a significant increase in mitosis abnormalities, increased frequency of aneuploidy involving chromosomes 12 and 17, marked reduction in cell proliferation, and increased autophagy and apoptosis (Souza et al., 2016). Animal and human brain cell organoid models supported the evidence that Zika virus can cross the placenta and induce brain abnormalities (Desai, Hartman, Jayarajan, Liu, & Gallicano, 2017; Janssens et al., 2018; Mittal et al., 2017; Nguyen et al., 2017; Nunes et al., 2016; Saiz et al., 2017). Surveillance studies have predicted the probability of microcephaly when a pregnant woman contracts a Zika virus infection as between 1.98% and 2.3% (Coelho & Crovella, 2017; Jaenisch et al., 2017).

The structure of the Zika virus was identified using cryoelectron microscopy (Faizan et al., 2016). It is a single-stranded, enveloped RNA virus composed of 10 proteins (three structural and seven nonstructural). Zika virus was identified as an arbovirus of the family *Flaviviridae*. Closely related viruses include dengue, West Nile, and yellow fever (A. Sharma & Lal, 2017). Two distinct lineages were identified: African and Asian. The current strain in the Americans is most closely related to the Asian lineage (Desai et al., 2017; McArthur, 2017).

Methods of transmission were identified. The primary mode of transmission is via infected mosquito bite. *Aedes aegypti*, *Aedes albopictus*, and multiple other mosquito species are known vectors (Petersen, Jamieson, Powers, & Honein, 2016; Rawal et al., 2016; A. Sharma & Lal, 2017). Sexual transmission has been documented, including unprotected male-to-female, female-to-male, and male-to-male. Zika virus has been detected in semen up to 188 days after the onset of symptoms (Saiz et al., 2017; A. Sharma & Lal, 2017). During the French Polynesian outbreak, Zika virus RNA was detected in 3% of asymptomatic blood donors (Musso et al., 2014). The first confirmed case of blood-transfusion-related Zika virus infection occurred in Brazil (A. Sharma & Lal, 2017). Vertical transmission between mother and fetus occurs. Zika RNA has been documented in amniotic fluid, placenta, and fetal brain tissue (Reagan-Steiner et al., 2017; Tschoeke, Oliveira, Leomil, Tanuri, & Thompson, 2017). Multiple studies involving animal models also demonstrated vertical transmission (Nguyen et al., 2017). Although Zika RNA and infectious viral particles have been detected in breast milk, no case of transmission related to breastfeeding has been documented (Cavalcanti et al., 2017; Colt et al., 2017; Sotelo et al., 2017).

Detection of Zika virus infection is complicated by multiple factors. Asymptomatic infection presents in up to 80% of those who tested positive for Zika immunoglobulin M (IgM) antibodies (Chua, Prat, Nuebling, Wood, & Moussy, 2017; A. Sharma & Lal, 2017). Even those with symptoms such as low-grade fever, maculopapular rash, arthralgia, headache, and conjunctivitis may fail to recognize and report the illness. Cross-reactivity between Zika, dengue, and chikungunya viruses confounds serum reverse transcription polymerase chain reaction (RT-PCR) testing. The optimal timing of tests is not known. Serum RT-PCR is positive for only a limited time during the first 3 to 7 days of symptoms (Adebanjo et al., 2017; Rabe et al., 2016; Rawal et al., 2016). Current definitive testing involves detection of IgM antibodies followed by a plaque reduction neutralization test ruling out dengue. This testing is labor-intensive and time-consuming, taking up to several weeks for final results (Adebanjo et al., 2017; Rabe et al., 2016; Shan et al., 2017). The results of IgM testing are not 100% indicative of a Zika infection during pregnancy: positive IgM results can reflect a pre-pregnancy exposure while negative IgM results can occur if testing occurred before the formation of antibodies (Adebanjo et al., 2017). The quest for a rapid, inexpensive test with adequate sensitivity and specificity continues.

The CDC recommendation for testing has evolved in response to expansion of the body of evidence and decline in prevalence creating increased risk for false-positive results. All pregnant women should receive screening questionnaires administered by a nurse or other healthcare provider to determine if there is a potential Zika infection risk due to travel by herself or her partner within a country with known Zika virus in the mosquito population. An updated map showing areas with a risk of Zika infection can be found at www.cdc.gov/zika/geo. The questionnaire also asks whether she or her partner has had any signs or symptoms of Zika infection. As of July 2017, the recommendation changed from testing all women who traveled to countries with known Zika virus infection to those who are symptomatic or have repeated exposure. Current recommendations may be found on the CDC website for Zika. The actual decision on whether to test is made based on discussion between the woman and her healthcare provider. The current recommendation on which test to provide can be found on www.cdc.gov/zika/hc-providers/testing-guidance.html (Adebanjo et al., 2017). In areas of active Zika infection, such as Puerto Rico in 2016, the recommendation may be for all pregnant women to be tested (D'Angelo et al., 2017).

The third stage of response to the Zika infection (Defense) is limited by a lack of effective treatments. The focus is on prevention with recommendations for mosquito control, prevention of mosquito bites, and limitation of travel by pregnant women to areas known to have Zika virus. Integrated vector management is used to describe steps for mosquito control. It includes elimination of breeding sites such as draining of swamps, elimination of free-standing water around homesites, insecticides, and use of *Wolbachia* bacteria and genetically modified male mosquitos to reduce reproduction (Rather, Kumar, Bajpai, Lim, & Park, 2017). Personal protection methods include use of insect repellants, wearing long sleeves and long pants, mosquito netting around beds, and screens on doors and windows. In January 2016, the CDC issued a travel notice advising pregnant women to avoid travel in areas of active Zika virus. The following precautions are recommended for the protection of the fetus from CZS: unintended pregnancies should be avoided, conception delayed by potentially exposed women for at least 8 months and potentially exposed men for at least 6 months, and abstinence or consistent condom use by those who live in/travel to those areas with active Zika virus (Peterson et al., 2016; Rather et al., 2017).

Development of a vaccine against the Zika virus is complicated by several factors. The population most at risk (pregnant women and their fetuses) necessitates strict adherence to safety protocols. There is a concern for the development of increased virulence of flavivirus infections due to antibody-dependent enhancement (ADE). ADE can occur with cross-reactivity to previous infections by a different closely related virus (dengue and chikungunya are endemic to the same areas as Zika). As of July 2017, at least 38 vaccines were in development with five advancing to phase 1 trials (Lagunas-Rangel, Viveros-Sandoval, & Reyes-Sandoval, 2017). Until a vaccine is developed, we will not reach stage 4 (De-escalation) in the Pattern of Response to Emerging Infections.

Until prevention is a viable option, we must be prepared to deal with the inevitable outcomes of CZS. Management of suspected Zika-exposed infants is described in Figure 26.1. Multidisciplinary specialists include any or all of the following: neurologists, ophthalmologists, infectious disease specialists, endocrinologists, geneticists, occupational therapists, audiology, orthopedics, and early intervention. Potential problems associated with CZS include developmental delays, seizures, impaired vision or hearing, dysphagia with associated feeding difficulties and growth restriction,

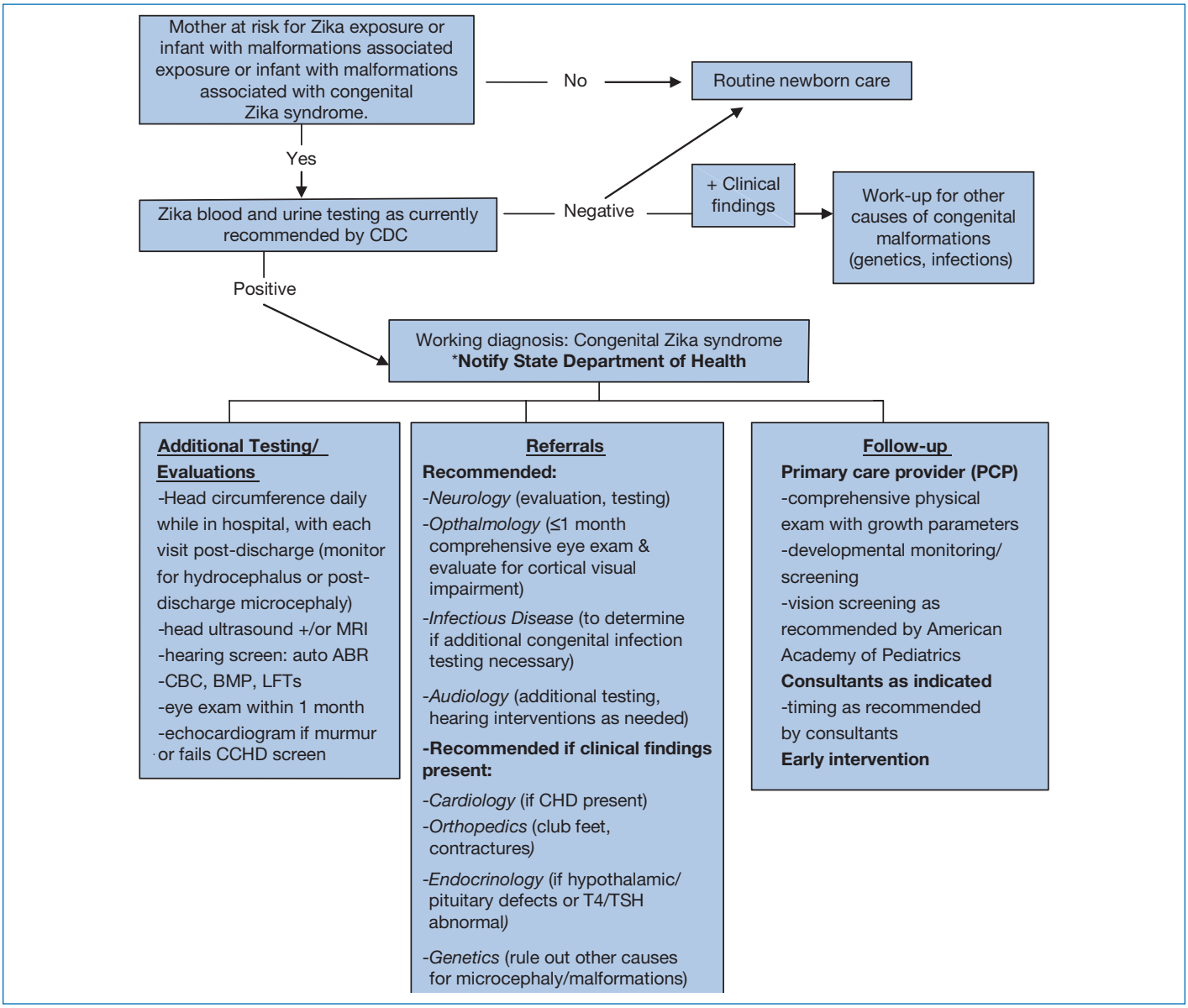

FIGURE 26.1 Zika risk algorithm.

autoABR, automated auditory brainstem response screen; BMP, basic metabolic panel; CBC, complete blood count; CCHD, critical congenital heart disease; CDC, Centers for Disease Control and Prevention; CHD, congenital heart disease; LFTs, liver function tests; T_4, thyroxine; TSH, thyroid-stimulating hormone.

Sources: Adapted from Adebanjo, T., Godfred-Cato, S., Viens, L., Fischer, M., Staples, J. E., Kuhnert-Tallman, W., & Moore, C. A. (2017). Update: Interim guidance for the diagnosis, evaluation, and management of infants with possible congenital Zika virus infection—United States, October 2017. *Morbidity and Mortality Weekly Report, 66*(41), 1089–1099. doi:10.15585/mmwr.mm6641a1; Women and Infants Pediatric Zika Algorithm. (2017). Retrieved from http://cnesites/sites/clinicianresources/wih/Shared%20Documents/Zika%20Algorithm.pdf

contractures requiring orthopedic interventions, and recurrent respiratory infections if diaphragmatic paralysis occurs (rare; Adebanjo et al., 2017; Leal, Muniz, Caldas Neto, et al., 2016; Leal, Muniz, Ferreira, et al., 2016; Satterfield-Nash et al., 2017; van der Linden, Pessoa, et al., 2016). **Quality and Safety: Current CDC recommendations for infants with clinical findings consistent with CZS include head ultrasound, automated auditory brainstem response (ABR), and comprehensive ophthalmology examination by 1 month of age** (Adebanjo et al., 2017). Postnatal microcephaly or hydrocephalus can develop, requiring close monitoring of head circumference (A. A. M. Silva et al., 2016). Following an examination by a neurologist, a CT or MRI may be indicated, allowing better evaluation of the structures of the brain. The clinician should monitor feedings for any difficulty coordinating suck/swallow/breathing, coughing or choking during feedings, and/or prolonged feeding times (Adebanjo et al., 2017). Occupational therapists may be able to assist with feeding difficulties, but gastrostomy tube feedings could be indicated for extreme cases. Seizures were present in 50% of a group of 48 infants with CZS in Brazil (A. A. M. Silva et al., 2016). If seizures are present, the neurologist will guide use of antiepileptics. Pessoa et al. (2018) reported that 100% of infants with CZS had motor abnormalities similar to cerebral palsy, demonstrating both pyramidal and extrapyramidal motor abnormalities. **Quality and Safety: Early intervention referrals are indicated. Emergency Alert: Rare cases of diaphragm paralysis may necessitate ventilatory support.** If arthrogryposis is present, physical therapy or serial casting by an orthopedist may be indicated. Family support is necessary as parents deal with a handicapped child. A summary of potential problems requiring follow-up is presented in Table 26.4.

TABLE 26.4

POTENTIAL PROBLEMS ASSOCIATED WITH CONGENITAL ZIKA SYNDROME REQUIRING CLOSE FOLLOW-UP POST-DISCHARGE

Specialty	Problem
Neurology	Hydrocephalus Seizures Sleep apnea Irritability Hypertonia/spasticity
Developmental specialists/ occupational therapists/physical therapists/feeding specialists/ speech therapists	Developmental delays Dysphagia, swallowing dysfunction Feeding difficulties
Nutritionist/lactation consultants/occupational therapists	Poor growth
Pulmonology/ENT	Aspiration Diaphragmatic paralysis
Endocrinology	Hypothalamic or pituitary dysfunction Thyroid disorders
Cardiology	Congestive heart failure if significant ventricular septal defect or atrial septal defect
Ophthalmology	Visual impairment
Audiology/ENT	Auditory impairment
Orthopedic/physical therapy	Clubfeet Hypertonia/spasticity

ENT, ear nose throat.

ANTIMICROBIAL RESISTANCE

Microorganisms demonstrate remarkable adaptability in response to antimicrobials. Penicillin was first used to treat human infections in 1941. Penicillin-resistant *Staphylococcus aureus* presented in 1944 and became widespread by the 1950s (Rice, 2006; Tenover, 2006). Today 95% of *S. aureus* is resistant to penicillin due to penicillinase production (A. J. Shah, Mulla, & Revdiwala, 2012). Resistant strains of bacteria develop as new antimicrobials are introduced. The mechanisms of resistance vary with the antimicrobial actions of each antibiotic. Not only do the mechanisms vary, but the organisms have developed ingenious methods of transferring this resistance, making even existing susceptible organisms capable of developing resistance.

Natural or intrinsic resistance refers to the innate characteristics of an organism which interfere with the action of an antibiotic. Gram-negative bacterial wall structure, which includes an outer cell wall in addition to the peptidoglycan membrane layer and an intermediate space, can limit the uptake of a drug. This is an example of natural resistance. Acquired resistance occurs when a formerly susceptible organism becomes resistant (Mulvey & Simor, 2009). MRSA is an organism with acquired resistance.

Some bacteria have developed mechanisms to block the antibiotic binding necessary to act on bacteria. Beta-lactam antibiotics (such as the penicillins, cephalosporins, and carbapenems) inhibit bacterial cell wall synthesis, specifically with the synthesis of the peptidoglycan layer (Patel & Saiman, 2010). Interference requires the antibiotic bind to the cell wall at a target site called the penicillin-binding protein (PBP). Certain organisms have acquired genes encoding enzymes called beta-lactamases which hydrolyze the amide bond of the beta-lactam ring and deactivate the antibiotic. Other organisms have evolved altered PBP structure, prohibiting the binding of the antibiotic (Arias & Murray, 2019; Baley & Leonard, 2013; Patel & Saiman, 2010). Carbapenems bind at a different site, PBP2. *Klebsiella pneumoniae* may produce carbapenamases which hydrolyze carbapenems, interfering with binding at that site (Puopolo, 2017). Bacteria may have one or multiple genes encoding for these methods.

Certain antibiotics must enter the microorganism in order to attach to a ribosome. They interfere with protein synthesis. Aminoglycosides, macrolides, and chloramphenicol are examples of these antibiotics. Passage through gram-negative bacteria walls often occurs through "porin" channels. Some bacteria have evolved the ability to close these porin (down-regulation), blocking the entrance into the microorganism. Other bacteria have evolved efflux pumps with the ability to push the antibiotic out of the cell (Cotten, 2016; Soto, 2009; Tenover, 2006).

Other characteristics of microorganisms may influence the development of resistance. Certain bacteria develop biofilms. The microorganisms associate with and adhere to submerged surfaces (such as indwelling catheters). They become enclosed with a matrix, extracellular polymers composed primarily of polysaccharides, binding the cells to the submerged surface and to each other. This matrix prevents or impedes the diffusion of antimicrobials to the bacteria and protects the microorganisms from host defenses. In addition, oxygen and nutrient diffusion is impaired, decreasing growth of the organisms themselves. Antibiotics that act on growth can be impaired (Baley & Leonard, 2013; Cotten, 2016; Patel & Saiman, 2010).

GENETIC MECHANISMS OF RESISTANCE

Natural or intrinsic resistance is stable and conferred by genes encoded in the chromosomal DNA. It is shared by all members of the genus. Acquired resistance involves a change in genetic material, either by mutation or by exchange of genetic material. Bacteria have multiple methods to exchange genetic material. Genetic material, including genes encoding for resistance, may exist outside of the chromosome on plasmids. Exchange of genetic material between bacteria occurs through conjugation, transduction, and transformation (Arias & Murray, 2019; Cantley & Milstone, 2015; Cotten, 2016; Johnson, 2012; Mulvey & Simor, 2009).

Conjugation involves the transfer of plasmids through elongated proteinaceous structures called sex pili, extending from the donor to recipient. Both donor and recipient have a copy of the plasmid. Transfer can be inter-species, even between gram-negative and gram-positive organisms (Cantley & Milstone, 2015; Tenover, 2006; Vrtis, 2008).

Transduction involves exchange of genetic material facilitated by viruses called bacteriophages. The genes may be of plasmid or chromosome origin. Transduction is a relatively rare event (Tenover, 2006; Vrtis, 2008).

Transformation involves acquisition of genetic material from the environment. When cell lysis occurs, DNA is released. The

DNA binds to the cell surface of another bacterium. The bound DNA is taken up through the cell membrane and incorporated into its chromosome or a plasmid within the bacteria (Arias & Murray, 2019; Cantley & Milstone, 2015).

Transposition enhances the spread of resistance. Genes may be flanked by insertion sequences at either end, creating a transposon. These transposons can "jump" to different locations on the chromosome or plasmids. A gene that was formerly on a chromosome or non-transferable plasmid can jump to a plasmid that can be exchanged between bacteria. This is the mechanism by which characteristics that are intrinsic to only one species can be transferred to a different species (Arias & Murray, 2019; Johnson, 2012).

In some cases, the gene that confers resistance requires exposure to the antibiotic before the gene is activated. Bacteria with inducible resistance may initially test susceptibility to an antimicrobial. With exposure to the antimicrobial, the gene is activated and begins to produce enzymes such as beta-lactamases, inactivating the antimicrobial (Patel & Saiman, 2010). The patient's condition worsens as the protected bacteria proliferate. The provider draws a second culture, and susceptibility shows the organism is now resistant to the original antibiotic.

PHARMACODYNAMICS AND RESISTANCE

Activity is measured based on minimal inhibitory concentrations (MICs) expressed in micrograms per milliliter. MIC is the lowest concentration of an antimicrobial agent that results in inhibition of bacterial growth. Antimicrobials are classified as either time-dependent or concentration-dependent. Time-dependent antimicrobials rely on serum concentrations that remain above the MIC for 60% to 70% of the treatment duration. These include beta-lactams and macrolides. Concentration-dependent antimicrobials rely on plasma concentrations within an area under the curve formed by plotting the plasma concentration of the drug versus time. Concentration-dependent antimicrobials include aminoglycosides, quinolones, and azalides (Andrews, 2003). Peak and trough drug levels are monitored for concentration-dependent medications. Peak/MIC ratio is used to describe optimal bactericidal effect based on higher peak concentration and increased dosing (Shea & Jacobi, 2009). Under-dosing increases the probability of developing resistant organisms (Cotten, 2016).

The MIC susceptibility breakpoints for antibiotic agents have been established and published by the Clinical and Laboratory Standards Institute. Ranges exist for mildly resistant and highly resistant organisms (Shea & Jacobi, 2009). Culture and susceptibility reports interpret an isolate's activity based on these standards. One confounding variable is the possibility of heteroresistance. Heteroresistance presents when a single strain of bacteria has both susceptible cells (such as MIC $\leq$ 2 mcg/mL for vancomycin) and intermediate resistant cells (MIC $\leq$ 4–8 mcg/mL for vancomycin; Patel & Saiman, 2010). This results in the chosen antibiotic only being effective for some of the bacteria, resulting in prolonged repeat positive cultures and extended length of treatment until the antibiotic is changed.

SELECTIVE ANTIBIOTIC PRESSURE

Selective antibiotic pressure is the trend for dominant antimicrobial species to evolve in response to the antibiotics chosen for treatment. Exposure to antibiotics creates an environment that inhibits or kills susceptible organisms but leaves resistant organisms alive and reproducing. Over time, resistant organisms may become the dominant species, colonizing the host. Within individual hospitals and the community, the specific antimicrobial selection can influence the development and predominance of resistant strains (Doyle, Buising, Thursky, Worth, & Richards, 2011; Mulvey & Simor, 2009). Indiscriminate over-the-counter use of antibiotics in China and Egypt may have contributed to third-generation cephalosporin resistance in those countries (Huang, Zhuang, & Du, 2007; Mohsen et al., 2017). Antimicrobials have also been used as a livestock growth promoter. Researchers found vancomycin-resistant enterococci (VREs) in the gut flora of poultry and swine (DeLisle & Perl, 2003; Shuford & Patel, 2005). Consumption of livestock colonized by antimicrobial-resistant organisms promotes spread of these organisms to humans (Collignon, Powers, Chiller, Aidara-Kane, & Aarestrup, 2009). The impact of selective antibiotic pressure is a guiding principle for antimicrobial stewardship.

METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS*

Neonates are exposed to and their skin subsequently colonized with *S. aureus* shortly after birth. Colonization can also occur in the nasopharynx and gastrointestinal tract. Eighty percent of infants are colonized by day 10 of life (Baley & Leonard, 2013; Bizzarro & Gallager, 2007). Of concern is the increasing prevalence of *S. aureus* which is resistant to third-generation cephalosporins and semi-synthetic penicillins such as methicillin. Premature and other compromised infants spend this early time period in NICUs where the selective pressure favors microorganisms with resistance. Outbreaks of MRSA infections were initially reported in the 1970s (Bizzarro & Gallagher, 2007). MRSA was first reported in an NICU in 1981 (Carey & Long, 2010; M. L. Gregory, Eichenwald, & Puopolo, 2009; Lessa et al., 2009; Sakamoto et al., 2010). MRSA outbreaks have now been reported throughout the world (Gregory et al., 2009; Huang et al., 2011; Jain, Agarwal, & Bansal, 2004; Kamath, Mallaya, & Shenoy, 2010; Lepelletier et al., 2009; Nambiar et al., 2003; Park, Seo, Lim, Woo, & Youn, 2007; Saiman et al., 2003; Seybold et al., 2008; Shirai et al., 2017; H. A. Silva et al., 2009). MRSA colonization rates vary by geographic location and institution, ranging from 1.3% to 50% (Azarian et al., 2016; Bizzarro & Gallagher, 2007; Carey, Della-Latta, et al., 2010; Carey, Duchon, Della-Latta, & Saiman, 2010; M. L. Gregory et al., 2009; Huang, Chou, Su, Lien, & Lin, 2006; Jain et al., 2004; Murillo, Cohen, & Kreiswirth, 2010; Nelson & Gallagher, 2012; Sarda et al., 2009; Seybold et al., 2008; Song et al., 2010). Infection rates following colonization range from 14.7% to 81% (Bizzarro & Gallagher, 2007; Carey, Duchon, et al., 2010; Gregory et al., 2009; Sarda et al., 2009; H. A. Silva et al., 2009; Song et al., 2010). From 1995 to 2004, the CDC National Nosocomial Infection Surveillance System (NNIS) reported that 23% of isolates causing infections in NICUs were methicillin-resistant (Lessa et al., 2009). The incidence of MRSA infection in the United States NICUs increased 300% from 1995 to 2004 (Blanchard, Quach, & Autmizquine, 2015; Cantley & Milstone, 2015; Lessa et al., 2009; Milstone, Song, Coffin, & Elward, 2010). Certain areas of the world such as Taiwan have such a high percentage (95%) as to be considered endemic (Huang et al., 2011).

Methicillin resistance is associated with specific genes: staphylococcal chromosome cassette (SCC) and *mecA*. The SCC gene complex and *mecA* gene confer resistance through changing the target site structure, creating (PBP)2A which has a low affinity for beta-lactam antibiotics (Blanchard et al., 2015; Carey & Long, 2010; Doyle et al., 2011; Lowy, 2019; Patel & Saiman, 2010).

MRSA infections are classified as either healthcare associated (HA-MRSA) or community acquired (CA-MRSA). Originally, HA-MRSA was the type more commonly seen in the NICU. Song et al.

(2010) reported 67% with HA-MRSA compared with 33% with CA-MRSA in their unit. CA-MRSA is gaining in prevalence (Baley & Leonard, 2013; Carey, Della-Latta, et al., 2010; M. L. Gregory et al., 2009). Pulse-field gel electrophoresis (PFGE) and polymerase chain reaction (PCR) allow identification of specific clones through molecular typing. Certain strains are associated with HA-MRSA. These strains differ in the type of SCC *mec* types: SCC *mecA* I to III. HA-MRSA strains include USA100, USA200, USA500 to USA800, and Rhine-Hessen (Healy, Hulten, Palazzi, Campbell, & Baker, 2004; Heinrich et al., 2011; Ramos et al., 2011; Seybold et al., 2008). Other strains are associated with CA-MRSA. These demonstrate SCC *mecA* IV to V. These include USA300 (majority), MW2, USA400, USA1000, and USA1100 (Carey, Della-Latta, et al., 2010; Carey, Duchon, et al., 2010; Healy et al., 2004; Nelson & Gallagher, 2012; Seybold et al., 2008). The two types of MRSA infections differ in their resistance to antibiotics with HA-MRSA more resistant than CA-MRSA. CA-MRSA is usually susceptible to more non-beta-lactam antibiotics such as trimethoprim-sulfamethoxazole, clindamycin, and quinolone agents (M. L. Gregory et al., 2009; Ramos et al., 2011; Yee-Guardino et al., 2008). CA-MRSA may present with higher virulence. Certain strains produce Panton-Valentine leukocidin (PVL) and enterotoxins. PVL in particular has been implicated in the production of cytotoxins that attack the cell membrane, causing necrosis and cell lysis. CA-MRSA can present with severe necrotizing pneumonia and furunculosis (Baley & Leonard, 2013; Carey & Long, 2010; Rice, 2006; Yee-Guardino et al., 2008). Surveillance of multiple units has shown an increase in incidence of CA-MRSA, with CA-MRSA acquired during birth while HA-MRSA is more likely to be acquired nosocomially (Azarian et al., 2016; Blanchard et al., 2015; Dolapo, Dhanireddy, & Talati, 2014; Nelson & Gallagher, 2012; Reich et al., 2016).

Routes of transmission are primarily horizontal with transfer from a colonized parent or healthcare worker, or transferred from a colonized patient through contaminated hands or equipment (Maraqa et al., 2011; Patel & Saiman, 2010). The anterior nares are a major site of MRSA colonization (Maraqa et al., 2011). Other sites of colonization include the umbilicus, groin, axillae, hands, ears, gastrointestinal tract, and sinuses (Heinrich et al., 2011; Maraqa et al., 2011). Although some disagreement exists, the majority of practitioners consider screening of nares or nasopharynx sufficient to identify carriers (Lepelletier et al., 2009; Maraqa et al., 2011). Detection is accomplished by either PCR or culture (Enomoto, Morioka, Morisawa, Yokoyama, & Matsuo, 2009; Francis et al., 2010). PCR has a turnaround time of hours as opposed to the 2 days required for culture (Francis et al., 2010). Francis et al. (2010) demonstrated that PCR had a sensitivity of 100% and specificity of 98%, recommending follow-up of positive results by culture. The necessity to culture all healthcare workers is controversial and usually confined to outbreaks (Grant, Charns, Rawot, & Benedetti, 2008). Transmission from healthcare workers is well documented (Burton, Edwards, Horan, Jernigan, & Fridkin, 2009; Heinrich et al., 2011; Seybold et al., 2008; Takei, Yokoyama, Katano, Tsukiji, & Ezaki, 2010). Transmission of MRSA from mother to infant has also been documented (Mongkolrattanothai, Mankin, Cranston, & Gray, 2010; Nelson & Gallagher, 2012). Horizontal transmission from siblings has also been implicated (Nelson & Gallagher, 2012). Hospitals report CA-MRSA vaginal colonization rate of 0.4% to 10.4% in pregnant woman (Carey & Long, 2010), indicating a potential for transmission at birth. A positive culture obtained shortly after birth occurred in 1.7% of infants in a German hospital and 1.9% in a New Jersey hospital, suggesting such a transmission (Murillo et al., 2010; Seybold et al., 2008). Cases of transmission of CA-MRSA from contaminated breast milk (Behari, Englund, Alcasid, Garcia-Houchins, & Weber, 2004) and from father to infant (Al-Tawfiq, 2006) have also been reported.

MRSA infections may present as bloodstream infections (positive blood culture), surgical site infections, cellulitis, pustulosis, pneumonia, conjunctivitis, or osteomyelitis. Meningitis, urinary tract infections, brain abscesses, and endocarditis are relatively rare (Carey & Long, 2010; Chuang et al., 2004; M. L. Gregory et al., 2009; Nelson & Gallagher, 2012; H. A. Silva et al., 2009). The NNIS survey of MRSA infections from 149 nurseries from 1995 to 2004 classified 31% as bloodstream infections, 18% pneumonia, 17% conjunctivitis, 14% skin and soft tissue, 4% surgical, and 10% other (Lessa et al., 2009). Skin infection outbreaks have been reported in multiple otherwise normal full-term nurseries (Carey & Long, 2010). As with any infection, death is a possible outcome (Chuang et al., 2004; Nelson & Gallagher, 2012). Symptoms remain the same as for any neonatal infection.

The majority of risk factors for MRSA infections also coincide with neonatal sepsis: extreme prematurity and low birth weight, indwelling central lines, prolonged hospitalization, endotracheal intubation, and previous exposure to antibiotics (Burton et al., 2009; Lessa et al., 2009; Maraqa et al., 2011; Nelson & Gallagher, 2012; Shirai et al., 2017). Parental nutrition and gavage feedings, nearly universal in premature infants, are also implicated (Nelson & Gallagher, 2012). The NNIS reports rates of 5.4 infections per 1,000 catheter days for infants 1,001 to 1,500 g and 9.1 per 1,000 catheter days for infants weighing less than 1,000 g (Perlman, Saiman, & Larson, 2007). Colonization with MRSA frequently precedes infection (M. L. Gregory et al., 2009; Maraqa et al., 2011; Milstone, Budd, et al., 2010). In a recent meta-analysis, Washam, Woltmann, Haberman, Haslam, & Staat (2017) found that the only consistent risk factors for colonization were a gestational age less than 32 weeks and a birth weight less than 1,500 g. Kaushik, Kest, Zauk, DeBari, and Lamacchia (2015) found that there was a 10-fold increase in risk of developing an infection if the infant was colonized. Meta-analysis by two different groups showed a relative risk of 24.2 to 37.75 as compared with non-colonized (Maraqa et al., 2011; Zervou, Zacharioudakis, Ziakas, & Mylonakis, 2014).

Quality and Safety: Vancomycin remains the gold standard of treatment. Standard dosing is dependent on postmenstrual age (gestational age plus postnatal age). Dosing interval decreases with increasing postmenstrual and postnatal age. Current online references are available for both dose and interval. Trough levels should be monitored during treatment. While a range of 7 to 15 mg/L usually results in a therapeutic MIC of 1 mg/L, some experts recommend trough levels of 15 to 20 mcg/mL when treating MRSA (Blanchard et al., 2015; Cantley & Patel, 2014; Truven Health Analytics, 2018). The practitioner adjusts dosing to maintain levels. Duration of treatment depends on the type of infection with most bacteremia requiring a 7- to 10-day course while osteomyelitis may require 6 to 8 weeks for treatment (Blanchard et al., 2015; Carey & Long, 2010). Infectious disease specialists may be consulted for guidance. In the event an infant is allergic to vancomycin or resistance develops, linezolid is an option. For fulminant cases gentamycin or rifampin may be added for synergy or better blood–brain barrier penetration (Blanchard et al., 2015; Carey & Long, 2010; Puopolo, 2017). Quinupristin-dalfopristin, linezolid, and daptomycin are also choices (Baley & Leonard, 2013). The monoclonal antibody tefibazumab has not been proven effective (Carey & Long, 2010). A Cochrane study meta-analysis showed no significant difference in the prevention of staphylococcal infections in very low birth weight infants when anti-staphylococcal immunoglobulins were administered (Nelson & Gallagher, 2012; Puopolo, 2017; P. S. Shah & Kaufman, 2009).

In addition to antibiotic coverage, additional measures are indicated to assure optimal outcomes. These measures include removal of indwelling catheters, drainage of any abscess, and documentation of sterilization of the bloodstream with follow-up blood cultures. The NICU team monitors the infant for any signs of osteomyelitis (Carey & Long, 2010).

Attempts to decolonize infants and care workers achieve varied results. Intranasal mupirocin for 5 days is one measure. Multiple courses of mupirocin may be required (Carey, Della-Latta, et al., 2010; Heinrich et al., 2011; Lepelletier et al., 2009). While chlorhexidine baths are often used in older patients (Doyle et al., 2011), concern over neurotoxicity and chemical burns limits its use in the neonatal population (Carey & Long, 2010; Saiman, 2016). Units that use hexachlorophene baths often limit its use to infants with a birth weight of 1,500 g or higher (Saiman, 2006) or more than 36 weeks gestation (Milstone, Budd, et al., 2010; Nelson, Bizzarro, Dembry, Baltimore, & Gallagher, 2014). The baths may have more of a role in decolonization of the healthcare worker. However, the REDUCE MRSA Trial (Randomized Evaluation of Decolonization vs. Universal Clearance to Eliminate Methicillin-Resistant *Staphylococcus aureus*) found Universal Clearance to have a 37% reduction in rates of MRSA-positive cultures and 44% reduction of MRSA-positive blood cultures. The Universal Clearance protocol consisted of 5 days of daily 3% chlorhexidine baths and twice daily nasal mupirocin (Climo et al., 2013; Nelson et al., 2014). At present, a survey of the U.S. NICUs showed that only 37% followed a decolonization protocol (Pierce, Lessler, Popoola, & Milstone, 2017). Chlorhexidine- and mupirocin-resistance has been developed in some strains of MRSA (Reich et al., 2016). Despite attempts to decolonize, many infants remain colonized at the time of discharge (Francis et al., 2010; Lepelletier et al., 2009; Reich et al., 2016). Contact isolation is usually maintained until a minimum of two consecutive cultures are obtained (Francis et al., 2010).

MRSA outbreaks can be particularly stubborn and require strict adherence to infection control methods and additional surveillance and isolation. In 2006, the Chicago Department of Public Health issued a consensus statement on control of MRSA in NICUs. These measures include strict adherence to hand hygiene with the availability of waterless, alcohol-based hand-hygiene products at bedside. **Quality and Safety: Hospital infection control professionals should provide education and direct observation to ensure adherence.** Nasopharyngeal surveillance cultures should be done on admission and then weekly. All positive cultures require contact precautions with gowns and gloves for all care and masks for suctioning. For nursing assignments, admissions can be cohorted in one group until cultures are available, infants with positive cultures in another group, and infants with negative cultures in a third group. Mupirocin has been used to decolonize MRSA-positive infants and healthcare workers. However, a recent decolonization program at Johns Hopkins showed no difference in the rate of positive MRSA infections pre- and post-intervention (Popoola et al., 2016). Culture of healthcare workers and the environment may be indicated. Molecular analysis such as PFGE should be performed to analyze the relationship between strains and identify potential reservoirs and areas of infection control breakdown (Gerber et al., 2006). Extreme outbreaks with high persistence may require closure of the unit to new admissions until the organism is eradicated. Restriction of transfer of colonized patients prevents further contamination of outlying hospitals. Song et al. (2010) documented a stepwise approach using many of the Chicago consensus recommendations which took over 4 years to eradicate an MRSA outbreak in their nursery. In a Taiwan NICU where MRSA is endemic, it took 7 years (Huang et al., 2011).

The financial burden of MRSA can be tremendous. M. L. Gregory et al. (2009) reported screening costs alone during a 7-year period were 1.5 million dollars at their hospital. Infections are associated with prolonged length of stay, increasing the cost of hospitalization.

EXTENDED SPECTRUM BETA-LACTAMASE (ESBL) PRODUCING ORGANISMS

ESBL-producing organisms were first discovered in 1983 in Germany (Huang et al., 2007). Gram-negative microorganisms that produce ESBLs include *Escherichia coli*, *Enterobacter cloacae*, *K. pneumoniae*, *Klebsiella oxytoca*, *Pseudomonas*, *Salmonella enterica*, and *Serratia marcescens* (Blaschke et al., 2009; Crivaro et al., 2007; O'Connor et al., 2017; Pessoa-Silva et al., 2002; D. Sharma et al., 2016; Stapleton et al., 2016). Colonization rates of ESBL-producing organisms range from 5% to 53.8%, varying by geographic location and individual institutions (Murki, Jonnala, Mohammed, & Reddy, 2010; Ofek-Shlomai et al., 2011; Pessoa-Silva et al., 2003; Shakil, Ali, Akram, Ali, & Khan, 2010; Tsai et al., 2016). Outbreaks have been reported worldwide (Abdel-Hady, Hawas, El-Daker, & El-Kady, 2008; Bagattini et al., 2006; Conte et al., 2005; Gundes et al., 2005; Huang et al., 2007; Iregbu & Anwaal, 2007; Kristóf et al., 2007; López-Cerero et al., 2008; Mesa et al., 2006; O'Connor et al., 2017; Otman, Cavassin, Perugini, & Vidotto, 2002; Stapleton et al., 2016). Jain, Roy, Gupta, Kumar, and Agarwal (2003) reported ESBL in 86.6% of *Klebsiella* species, 73.4% of *Enterobacter* species, and 63.6% of *E. coli* strains causing infections in their nursery in India. The NNIS reported similar rates of ESBL resistance: 81.8% of *Klebsiella* species, 73.1% of *E. coli*, and 60% of *Enterobacter* species (Kamath et al., 2010). ESBL resistance has spread to *Neisseria gonorrhoeae* (Tapsall, 2009).

As previously described, beta-lactamase enzymes deactivate beta-lactam antibiotics through hydrolyzing the amide bond of the beta-lactam ring (Abdul-Hady et al., 2008; Huang et al., 2007; Mulvey & Simor, 2009; Shea & Jacobi, 2009). These enzymes extend resistance beyond penicillin to the extended-spectrum cephalosporins (ceftazidime, cefotaxime, ceftriaxone, etc.) and aztreonam (Abdel-Hady et al., 2008). Beta-lactamase enzymes make two of the four most common empirically prescribed antibiotics ineffective: ampicillin and cephalosporins. Inadequate empirical treatment is associated with higher mortality (Abdel-Hady et al., 2008; Maragakis, 2010; Shea & Jacobi, 2009).

Most ESBLs are encoded on genes located on plasmids, promoting the transfer of resistance between bacteria of the same and other species (Crivaro et al., 2007). Identified genes associated with ESBL include *SHV*, *TEM*, *CTX-M*, and *OXA* (Abdel-Hady et al., 2008; Blaschke et al., 2009; Kristóf et al., 2007; O'Connor et al., 2017; Tsai et al., 2016). Crivaro et al. (2007) demonstrated the same plasmid in both *S. marcescens* and *K. pneumoniae* during the investigation of ESBL in their NICU, indicating probable conjugal transfer of the plasmid between the two species. Other gram-negative bacilli may have chromosomal mutations which produce the gene *AmpC*, causing overproduction of beta-lactamase enzymes and making them resistant to even the beta-lactamase–beta-lactamase-inhibitor combination drugs (Kanj & Kanafani, 2011; Mulvey & Simor, 2009).

ESBL transmission can be either horizontal or vertical. Seale and Millar conducted a systematic review and found four documented cases of perinatal vertical transmission as of 2014. The reported prevalence of ESBL-producing *E. coli* in pregnant women ranges from 5% to 20% (Seale & Millar, 2014). The majority of neonatal

cases are transmitted horizontally. Horizontal transfer from contaminated patients through healthcare workers has been documented through PFGE analysis (Abdel-Hady et al., 2008; Boszczowski et al., 2005; Otman et al., 2002). Artificial fingernails on healthcare workers have been implicated in adult outbreaks (Boszczowski et al., 2005). Measures to control outbreaks are similar to those previously described for MRSA: strict hand hygiene, contact isolation, and cohorting of patients. Clinical improvement and sterilization of the bloodstream by antibiotics do not necessarily protect the gastrointestinal tract from colonization (Gundes et al., 2005). Screening for colonization is by stool or rectal culture (N. Singh et al., 2002). In contrast with MRSA, there is no reliable process for decolonization of carriers (Seale & Millar, 2014).

Risk factors for infection with ESBL-producing organisms include lower gestational age, low birth weight, and longer length of stay. Previous exposure to third-generation cephalosporins has been implicated in all studies. Mixed results were found for endotracheal intubation duration (Jain et al., 2003; Kristóf et al., 2007; Ofek-Shlomai et al., 2011; Pessoa-Silva et al., 2003; Shakil et al., 2010). In contrast with MRSA, only one of the studies found the presence of a central line to be a risk factor (Pessoa-Silva et al., 2003). Colonization frequently precedes infection (Crivaro et al., 2007). Infections with ESBL-producing bacteria are associated with increased costs, prolonged length of stay, and higher mortality rates (Abdel-Hady et al., 2008; Gundes et al., 2005; Iregbu & Anwaal, 2007; Scheans, 2010).

Treatment is guided by susceptibility to antibiotics. Many of the ESBL-producing organisms are less susceptible to beta-lactam–beta-lactamase inhibitor combinations due to higher production of ESBLs (Huang et al., 2007). Carbapenems are often first-line agents used to treat ESBL-producing organisms (Kanj & Kanafani, 2011). Synergy with gentamycin allows the beta-lactam antibiotic to be therapeutic in some cases of low resistance (Arias, Contreras, & Murray, 2010).

VANCOMYCIN-RESISTANT ENTEROCOCCUS

VRE was first reported in 1986 in Europe (DeLisle & Perl, 2003). By 2004, VRE strains accounted for 28.5% of enterococci (Bizzarro & Gallagher, 2007). VRE strains have been found in *Enterococcus faecium* and *Enterococcus faecalis* (Rice, 2006).

Enterococci have intrinsic resistance to many antimicrobials. They have long been resistant to beta-lactam antibiotics as they produce low-affinity PBP5, interfering with the binding of the antibiotic to the cell wall. They can also bypass the block of folic acid synthesis by extracting folinic acid derivatives directly from their environment, interfering with trimethoprim-sulfamethoxazole. Aminoglycosides have difficulty crossing the cell wall unless paired with beta-lactams for synergy. Enterococci also produce enzymes that modify the ribosomes, decreasing the binding and bactericidal activity. Macrolides cannot stop protein synthesis because of a modified ribosomal target (Arias & Murray, 2019; DeLisle & Perl, 2003; Tenover, 2006). Concern develops when acquired resistance occurs to one of the few antibiotics that was previously successful: vancomycin.

Vancomycin resistance is attributed to multiple gene clusters (*vanA* to *vanZ*), with *vanA* and *vanB* most significant (Arias & Murray, 2019). These clusters are associated with transposons that can move from chromosome to plasmids and transfer readily between bacteria. Glycopeptides normally interfere with cell wall synthesis by binding to the D-alanyl-D-alanine terminus of a pentapeptide cell wall precursor. Resistance is conferred by substituting D-ala-D-lactate depsipeptide instead of the D-alanyl-D-alanine, interfering with vancomycin binding and allowing cell wall synthesis to continue (Arias & Murray, 2019; DeLisle & Perl, 2003; Mulvey & Simor, 2009).

Transmission of VRE is horizontal with transfer from colonized patients. VRE generally colonizes the gastrointestinal tract. Screening involves stool, rectal, or perirectal cultures. Patient-to-patient transfer can occur through contamination of healthcare workers' hands. The hospital environment provides many potential fomites, with survival of VRE up to 5 weeks (DeLisle & Perl, 2003; Mulvey & Simor, 2009; N. Singh & Valsangkar, 2016). Known cases require contact isolation until three stools obtained 1 week apart remain negative (DeLisle & Perl, 2003). Risk factors for infection include prior antimicrobial therapy with vancomycin or broad-spectrum cephalosporins, prolonged hospitalization, and invasive procedures (Akturk et al., 2016; Louie, 2011; Mulvey & Simor, 2009).

Treatment of VRE is challenging and often involves a combination of agents. Microbial susceptibilities should guide treatment. Bacteriostatic agents such as chloramphenicol may need to be used (Bizzarro & Gallagher, 2007; DeLisle & Perl, 2003). Limited data suggest that linezolid may be effective in some neonates (Bizzarro & Gallagher, 2007). Linezolid is an oxazolidinone antibiotic that interferes with ribosomal protein synthesis (Arias et al., 2010). Multiple blood cultures are recommended to confirm sterilization of the bloodstream (DeLisle & Perl, 2003). VRE is associated with higher mortality (Bizzarro & Gallagher, 2007). Methods to control outbreaks are similar to those described for MRSA: strict hand hygiene, screening, isolation, cohorting of patients and nurses, and environmental decontamination (DeLisle & Perl, 2003).

MULTIDRUG-RESISTANT ORGANISMS

Multidrug-resistant organisms (MDROs) are gram-negative bacteria which are resistant to more than two classes of antimicrobials. These organisms are typically resistant to penicillins, cephalosporins, fluoroquinolones, and aminoglycosides. Some have developed resistance to carbapenems, making treatment options difficult (Mohsen et al., 2017; Mulvey & Simor, 2009; Puopolo, 2017). MDROs include some strains of *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *E. coli*, *E. cloacae*, *K. pneumoniae*, *K. oxytoca*, *Staphylococcus capitis*, and *S. marcescens* (Butin, Martins-Simões, Rasigade, Picaud, & Laurent, 2017; Mammina et al., 2007; Mohsen et al., 2017; Mulvey & Simor, 2009; Shea & Jacobi, 2009; Simões et al., 2016). These organisms often have multiple mechanisms for resistance. Energy-dependent efflux pumps located on the cytoplasmic membrane are encoded on the *MexB* gene. Regulation of outer membrane porin is encoded on the *OprM* gene. A protein joins these genes and is designated MexA. These combine to form the gene complexes *MexAB-OprM*, *MexXY-OprM*, *MexCD-OprJ*, and *MexEF-OprN* (Tenover, 2006). Efflux systems work against multiple classes of antimicrobials by lowering the concentration within the cell to a subtherapeutic level. Many already produce beta-lactamases, causing resistance to penicillins and cephalosporins (Mammina et al., 2007). A carbapenem-resistant gene, *VIM11*, has been identified (Mammina et al., 2007). Carbapenemase production occurs in some species of *E. coli* and *K. pneumoniae* (Cantley & Milstone, 2015; Kanj & Kanafani, 2011). Simões et al. (2016) found a *S. capitis* strain that carries a gene (*nsr*) which confers resistance to nisin, a bacteriocin secreted by an organism in the gut microbiota.

The usual reservoir of MDROs is the gastrointestinal tract. Screening is via stool culture. The proportion of colonized MDROs varies by geographic location and individual NICUs, ranging from 12% to 55.2% in nurseries with surveillance systems geared to

detect these organisms (Giuffrè et al., 2016; Mammina et al., 2007; A. J. Shah et al., 2012; Tsai et al., 2014). Colonization is a risk factor for infection (Giuffrè et al., 2016). Breast milk proved protective in one study. Transfer is horizontal from patient-to-patient via contaminated healthcare workers' hands or the environment. Identified risk factors for infection include early gestational age, low birth weight, use of invasive devices, and longer duration of NICU stay (Giuffrè et al., 2016; Mammina et al., 2007).

MDROs have caused conjunctivitis, pneumonia, bloodstream infections, and death (Scheans, 2010). Treatment of MDROs should be guided by susceptibilities and may involve a combination of antimicrobials that are normally considered bacteriostatic instead of bactericidal. Clinicians may be forced to use antimicrobials that have few studies of the pharmacodynamics in neonates. Partnership between neonatologists, clinical pharmacists, and infectious disease specialists may present the best management. Outbreaks are managed through a combination of effective hand hygiene, isolation, cohorting of patients and nurses, and environmental decontamination (Giuffrè et al., 2016; Maragakis, 2010).

Babesia

Babesia is an example of a pathogen with an animal vector, which has been recognized by new detection methods as causing human infection (Stramer et al., 2009). Like Lyme disease, it is tick-borne and found primarily in certain geographic locations. *B. microti*, the most common species, is an intraerythrocytic protozoa which is detected by finding characteristic ring forms within the blood cell on blood smears (Aderinboye & Syed, 2010; Fox et al., 2006; Herwaldt et al., 2011; Raju, Salazar, Leopold, & Krause, 2007; Snow, 2009). It can also be detected by PCR or serologic immunofluorescent antibody testing (Aderinboye & Syed, 2010; Fox et al., 2006; Graham, Stockley, & Goldman, 2011; Simonsen, Harwell, & Lainwala, 2011). In 2008, the Food and Drug Administration (FDA) identified *B. microti* as the most frequent transfusion-transmitted microbial pathogen in the United States (Levin & Krause, 2016).

Most cases of human babesiosis are associated with deer tick bites. Babesiosis is most common in five Northeastern states: Connecticut, Massachusetts, Rhode Island, New York, and New Jersey. It has also been found in two Midwestern states, Minnesota and Wisconsin. It is primarily associated with the species *B. microti* (FDA, 2018; Hoffman, 2018). Other areas of the country such as the Pacific Northwest (Washington and California) are associated with a different species, *B. duncani* (Herwaldt et al., 2011). In contrast, the majority of neonatal infections are the result of blood transfusions from asymptomatic donors (Fox et al., 2006; Herwaldt et al., 2011). The first documented neonatal case occurred in 1982 (Raju et al., 2007). As of October 2011 there have been 18 neonatal cases (Herwaldt et al., 2011). Seven infants in a NICU acquired babesiosis from transfusions from two infected donors (Simonsen et al., 2011). There have been two reported congenital infections transmitted from a mother with babesiosis (Aderinboye & Syed, 2010; Fox et al., 2006). There are two reported cases of infants acquiring the infection post-discharge, with ticks removed from their bodies 2 weeks prior to the development of symptoms (Fox et al., 2006).

Babesiosis in neonates presents with jaundice, hepatosplenomegaly, hemolytic anemia, occasional thrombocytopenia, and occasional conjugated hyperbilirubinemia (Aderinboye & Syed, 2010; Fox et al., 2006). Unlike adult cases, fever is only reported in some cases (Aderinboye & Syed, 2010). Treatment includes the combination of clindamycin and quinine or the combination of azithromycin and atovaquone. Response is usually rapid with reduction or clearing of parasites within a few days. Treatment is continued for 7 to 14 days (Aderinboye & Syed, 2010; Fox et al., 2006; Raju et al., 2007; Simonsen et al., 2011). Packed red blood cell transfusions may be required for anemia. In severe cases an exchange transfusion may prove beneficial (Aderinboye & Syed, 2010; Fox et al., 2006; Simonsen et al., 2011). Cardiac monitoring will identify any arrhythmias, a potential adverse reaction associated with quinine (Raju et al., 2007). Hearing screening should follow treatment with quinine as hearing loss and tinnitus are potential adverse reactions reported in adults (Snow, 2009).

In March 2018, the FDA approved the first screening test for *Babesia*. The FDA plans to release guidelines for testing later in the year (FDA, 2018; Hoffman, 2018). Prior to this, blood banks relied on screening of donors for babesiosis by questionnaire only, with only known cases excluded, and a question about exposure to tick bites not routinely included (Germain & Goldman, 2002). Asymptomatic donors with babesiosis remain undetected. The true extent of neonatal *Babesia* exposure may be higher with asymptomatic infants undiagnosed. In addition, leukoreduction and irradiation are not effective against *Babesia* (Simonsen et al., 2011). Until the blood supply is routinely screened, transfusion blood products for infants may be screened for babesiosis similar to our screening for cytomegalovirus (Hoffman, 2018).

MEASLES

Measles is an example of a disease that is re-emerging. Prevention is managed through a series of two vaccinations: the first at 12 to 15 months and the second at 5 to 6 years. Parents may elect to decline immunization, and their child may be protected by herd immunity. A paper from Italy documents seven cases of measles in infants: four were less than 3 months and three were less than 12 months. Four of the mothers had no immunization and contracted measles themselves, while the other cases involved siblings with the disease (Bozzola et al., 2011). Of concern with infants is the case-fatality rates are increased in children younger than 5 years and in the immune-compromised (The Committee on Infectious Diseases American Academy of Pediatrics, 2015b, p. 535). Infants who are exposed to measles will require respiratory isolation. There is no specific antiviral therapy (The Committee on Infectious Diseases American Academy of Pediatrics, 2015b, p. 536).

COMBATING EMERGING INFECTIONS

The war against emerging infections begins with infection control. Many of the infection control methods such as isolation, cohorting patients, and surveillance are described in the "Methicillin-resistant *Staphylococcus aureus*" section. The goal of infection control is to reduce and control reservoirs. Hand hygiene remains an important action to protect the patients (Cantley & Milstone, 2015; Higgins, Baker, & Raju, 2010; N. Singh & Valsangkar, 2016). The use of alcohol-based gel disinfectants at the bedside improves compliance (Saiman, 2006; Sakamoto et al., 2010; N. Singh & Valsangkar, 2016). Steps to minimize overcrowding and understaffing also assist. The American Academy of Pediatrics recommends a minimum of 150 square feet for each critically ill infant (Cantley & Milstone, 2015). Many NICUs have switched to a private room layout. Understaffing was the most frequent predisposing factor reported in a meta-analysis of 75 outbreaks of ESBL (Stapleton et al., 2016).

Care bundles are a group of evidence-based actions that when implemented together have been successful in reducing infections. Central Line-Associated Blood Stream Infections

(CLABSI) and Ventilator-Associated Pneumonia (VAP) are examples of care bundles (Doyle et al., 2011; Toth, Chambers, & Davis, 2010). A typical CLABSI bundle includes hand hygiene, use of full barrier precautions during line insertion, effective skin antisepsis at the insertion site, minimizing catheter entry and disinfecting hub with alcohol when entry is required, use of closed medication systems, daily fluid and tubing changes using sterile technique, infection surveillance, and removal of catheter when appropriate (Doyle et al., 2011; Garland et al., 2008; Saiman, 2006; N. Singh & Valsangkar, 2016). Removal of unnecessary catheters in particular is important as catheter duration is a risk of CLABSI. Sengupta, Lehmann, Diener-West, Perl, and Milstone (2010) reported that incidence of CLABSI increased by 14% per day during the first 18 days, decreased by 20% during day 19 through 35, then increased by 33% per day after 35 days. A survey of NICUs reporting CLABSI data to the National Healthcare Safety Network in 2009 showed that the majority followed a CLABSI bundle of some type (Hocevar et al., 2014). Hawes and Lee (2018) reported a decline in the incidence of CLABSI from 4.4 to 1.5 per 1,000 line days following implementation of a CLABSI bundle in their institution. VAP bundles have been implemented in some NICUs. A VAP bundle in the NICU might include hand hygiene, the use of in-line suction devices, limitation of saline administration, providing oral care with sterile water, planned extubation when readiness is achieved, and surveillance (N. Singh & Valsangkar, 2016).

Neonatal care providers continuously seek strategies to reduce the likelihood of colonization by antibiotic-resistant organisms. The use of probiotics is one strategy under investigation. The theory behind probiotics is viable nonpathogenic bacteria, such as *Lactobacillus acidophilus* or *Bifidobacterium infantis*, fed enterally to compete with potential pathogen-producing antibiotic-resistant organisms. Results of studies are mixed, with optimal dosing, organism type, and effectiveness to be established (Patel & Saiman, 2010; Saiman, 2006). The use of breast milk is protective, with decreased incidence of necrotizing enterocolitis and other infections documented. Breast milk contains 23 to 130 different oligosaccharides, a substance utilized by bifidobacteria. Lactoferrin in breast milk has anti-inflammatory, antimicrobial, and immunomodulatory properties (Higgins et al., 2010).

One strategy to reduce infections is the development of vaccines. This strategy effectively reduced the incidence of *Haemophilus influenza* serotype b disease by 99% after it was introduced in 1990. Less than one case per 100,000 children under 5 years old contract this disease after the introduction of the immunization program (CDC, 2008). Vaccine development is a goal in the fight against HIV. Infants remain at risk worldwide from perinatal transfer and through breastfeeding. A vaccine would be a lower cost alternative to detection and treatment of the disease. Research is in early stages, with safety and efficacy yet to be established.

The symptoms of sepsis are nonspecific in neonates, resulting in empiric treatment prior to obtaining a negative blood culture. Improved detection methods may help distinguish those episodes that are most likely sepsis-related from those that are related to other causes. Adjunctive tests such as C-reactive protein, procalcitonin, or interleukin-8 may help to distinguish cases of sepsis (Cantley & Patel, 2014; Higgins et al., 2010; Patel et al., 2009; N. Singh & Valsangkar, 2016; Zingg et al., 2011). Early detection also allows streamlining of antibiotics to those most likely to treat the microorganism. PCR tests are under investigation for some microorganisms such as group B *Streptococcus*, *E. coli*, *Candida albicans*, and MRSA (Enomoto, Morioka, Morisawa, Yokoyama, & Matsuo, 2009; Francis et al., 2010).

ANTIMICROBIAL STEWARDSHIP

Antimicrobial stewardship is the cornerstone in the battle against antimicrobial resistance. It is defined as "the optimal selection, dose, and duration of an antimicrobial that results in the best clinical outcome for the treatment or prevention of infection, with minimal toxicity to the patient, and minimal impact on subsequent resistance" (Lipsett, 2008; Louie, 2011). The goal of such a program is to preserve the effectiveness of prescribed antimicrobials by reducing resistance. Additional benefits include a reduction in costs, fewer antibiotic-related adverse events, and shorter hospital length of stay (Di Pentima & Chan, 2010; Louie, 2011; Newland & Hersh, 2010). Core strategies of antimicrobial stewardship include monitoring antimicrobial prescription and infectious agents, providing practitioners with feedback on this monitoring, and restricted use of certain antimicrobials to protect their effectiveness. Additional strategies include education, development of guidelines and policies, use of tools such as computerized order entry or automatic stop orders, dose optimization, cycling of antibiotics, and de-escalation of therapy (K. E. Gregory, 2016; Newland & Hersh, 2010). A multidisciplinary team is a key component for many antimicrobial stewardship programs. Membership can include pharmacists, infectious disease specialists, neonatologists, nurses, hospital epidemiologists, and bioinformatics specialists (Cantley & Patel, 2014; K. E. Gregory, 2016; Patel & Saiman, 2010; N. Singh & Valsangkar, 2016). Programs can be highly structured with formulary restriction, preauthorization requirements, and computerized order templates (Lipsett, 2008; Louie, 2011). Medical providers prefer programs that offer guidance over those which restrict prescriptive privileges (Patel, Rosen, Zaoutis, Prasad, & Saiman, 2010).

Principles of appropriate antimicrobial usage include prescribing only when clinically indicated, basing empiric antimicrobial selection on local flora and antimicrobial resistance patterns, adjusting antimicrobials according to susceptibilities obtained and within as narrow of coverage as to be effective, assuring dose and timing provide therapeutic levels for the required duration, and stopping the drugs as soon as appropriate (Hart, 2011; McPherson, Liviskie, Zeller, Nelson, & Newland, 2018). It is estimated that antibiotic use is unnecessary or inappropriate in 50% of treatment episodes (Fishman, 2006). Patients and families can pressurize practitioners to prescribe antimicrobials when they are not needed. Past practice in pediatrics included prescribing antibiotics for respiratory illnesses which were most likely viral and not affected by the antibiotics (Hart, 2011). This resulted in microorganisms exposed to many antimicrobials in their environment, contributing to the selective pressure favoring resistant organisms. **Emergency Alert: Inappropriate or excessive use of antibiotics has been linked with the development of MDROs, necrotizing enterocolitis, late-onset sepsis, or death** (Cantley & Patel, 2014; K. E. Gregory, 2016). Infectious disease committees for hospitals, states' departments of health, and various surveillance systems tabulate statistics on infectious agents and their antimicrobial resistance patterns. This information can guide choice of empiric antibiotics. While early-onset infections are initially treated with ampicillin and gentamycin, late-onset infections' empiric choice reflect broad-spectrum coverage of those microorganisms most likely to cause infection. In the past, this empiric choice often involved a cephalosporin, contributing to the selective pressure for ESBL-producing microorganisms. Once culture and sensitivity results are obtained, adjust antimicrobial coverage to monotherapy with a narrower activity if possible (Fishman, 2006; N. Singh & Valsangkar, 2016). Infection with multiple microorganisms may require multiple antibiotics (Vrtis, 2008). Failure to adjust to an

appropriate antimicrobial can contribute to increased morbidity and mortality (Cantley & Patel, 2014). Monitoring of drug levels and compliance with recommended dose and frequency based on gestational and postconceptual age promotes maintenance of levels above the MIC. Subtherapeutic levels will target susceptible microorganisms while allowing resistant agents to proliferate. Suspected infections are generally screened by blood culture and covered by empiric antibiotics. Practitioners should stop antibiotics if cultures fail to turn positive in 48 hours, limiting unnecessary environmental exposure. Duration of antimicrobial coverage is governed by the type of infection and proof of sterilization of the infected site. Any protracted exposure beyond that necessary to treat the infection contributes to the selective pressure for resistance.

In an era of rising resistance and limited development of new classes of antimicrobials, it is essential to protect the effectiveness of the current antimicrobials. **Quality and Safety: Restricted use of certain antimicrobials is a strategy to reduce resistance.** Vancomycin is the most commonly restricted drug as it is associated with the development of VRE (Cotten, 2016; Hammer, Lardieri, & Morgan, 2016; Louie, 2011). Several studies (Chiu et al., 2011; K. E. Gregory, 2016; McPherson et al., 2018) showed no increase in morbidity or mortality when vancomycin use was restricted to specific indications and no longer used for general empiric therapy. A vancomycin restriction policy at a Delaware children's hospital reduced the incidence of VRE (Di Pentima & Chan, 2010). Its effectiveness in treating infections caused by ESBL-producing microorganisms is another reason to protect it. The Committee on Infectious Diseases of the American Academy of Pediatrics (2015a, p. 875) recommends vancomycin use be limited to cases of MRSA. Other antimicrobials that may be restricted include carbapenems, linezolid, and fourth-generation cephalosporins. The substitution of beta-lactam–beta-lactamase inhibitors for cephalosporins resulted in decreased prevalence of ESBL-producing pathogens in a nursery in Korea (Lee et al., 2007). Restriction of cephalosporins in a nursery in India led to a 22% reduction in ESBL-producing gram-negative bacteria (Murki et al., 2010). Restrictions may come in the form of guidelines, preauthorization, or post-prescription review (Louie, 2011). Antibiotic cycling is another strategy. This cycling is a scheduled rotation of two or more antibiotic classes with similar range of activity over a specific time period, eventually returning to the original antibiotic class. Time periods vary from 1 to 4 months. The theory behind cycling is to reduce the selective pressure by limiting the exposure time to a particular antibiotic class. Evidence has not supported this strategy (Patel & Saiman, 2010; Puopolo, 2017).

Optimizing antimicrobial therapy involves tailoring dosing and method of antimicrobial administration to take advantage of the drug's pharmacodynamics. In the neonatal field, this is an area of evolution requiring current knowledge of recommendations. The use of yearly updated references such as Red Book or Micromedex Pediatric and Neofax Standard, both online resources, can assist in maintaining current knowledge. Clinical pharmacists who attend rounds with the care team are also resources. Potential alternate dosing regimens include continuous infusion or prolonged intermittent infusion. These alternate dosing methods can be effective for time-dependent antimicrobials, increasing the total time above the MIC (Shea & Jacobi, 2009). Inhaled antibiotic administration offers the potential for local action with minimal systemic adverse effects. Intermittent aerosolized administration of antibiotics has been used in older patients with *P. aeruginosa* pneumonia, particularly in patients with cystic fibrosis (Kanj & Kanafani, 2011). Antimicrobial stewardship promotes appropriate antimicrobial prescription through recommendations on antibiotic choice to narrow down the therapy and eliminate redundancy, monitoring effectiveness and providing reminders when antibiotics should be stopped (The Committee on Infectious Diseases American Academy of Pediatrics, 2015a).

Monitoring is another essential component of antibiotic stewardship. Days of therapy (DOTs) adjusted for 1,000 patient-days of hospitalization is a measurement of antibiotic utilization often used as a benchmark between NICUs (Cantley & Patel, 2014; K. E. Gregory, 2016). DOTs are often utilized to evaluate the effectiveness of broad-spectrum antibiotic reduction programs. Monitoring of infectious agents allows use of a NICU-specific antibiogram-guiding empiric antibiotic therapy. Monitoring of individual cultures allows reduction of duration of antibiotic use when cultures are negative and adjustment of appropriate antibiotic use when sensitivities are available (Cantley & Patel, 2014).

SUMMARY

Use of a conceptual framework, Pattern of Response to Emerging Infections, makes understanding emerging infections easier. It gives us an idea of where we stand in regard to the fight against specific pathogens. The conceptual framework can be applied to future outbreaks.

Sepsis and the steps to reduce it are a part of the NICU life. When acuity increases and the census rises, a heavy workload makes it easy to forget compliance with those mechanisms that protect our patients. Hand hygiene, isolation precautions, and surveillance are a necessary burden. Antimicrobial stewardship offers many benefits, including reduction of antimicrobial resistance. We may not be able to eliminate resistant organisms, but we can limit their spread and slow down their development.

Thirty-five years ago, the emerging infectious disease was HIV, an evolved zoonotic pathogen. Fifteen years ago, the emerging diseases focused on antimicrobial-resistant microorganisms. Today's emerging infection, Zika virus, is a different zoonotic pathogen. Tomorrow's emerging pathogens will be equally challenging. Development of new diagnostic tests and antimicrobial agents remain important and will involve research within and outside of the NICU.

EVIDENCE-BASED PRACTICE BOX

The practices used to control the spread of infectious diseases within a hospital setting have been evaluated for strength of evidence by the Hospital Infection Control Practice Advisory Committee of the Centers for Disease Control and Prevention and the Chicago-area Neonatal MRSA Working Group (Newman, 2016). The quality of evidence is rated I, II, or III. The highest quality, I, has one or more randomized trials with clinical outcomes supporting the evidence. Quality II is supported by one or more well-designed, non-randomized, or observational cohort studies with long-term clinical evidence. Quality III evidence is supported by expert opinion. Recommendations are rated A (strong evidence), B (moderate evidence), or C (optional based on existing evidence). Categories combine quality and strength of evidence (Table 26.5).

(*continued*)

EVIDENCE-BASED PRACTICE BOX (*continued*)

TABLE 26.5

EVIDENCE-BASED INFECTION CONTROL PRACTICES

Category	Infection Control Practice
IA	Hand hygiene (including periodic monitoring)
IA	Isolation of culture-positive patients
IA	Environmental support (bedside alcohol-based cleanser, adequate room/space for isolation, isolation supplies, environmental cleaning practices)
IA	Administrative support (organize data and reporting, adequate staffing)
IB	Contact isolation precautions
IB	Surveillance—scheduled screening for colonization
IB	Consider strain identification (molecular analysis)
IB	Infectious disease consultation
IB	For epidemics, consider halting admissions to unit until current patients are discharged
IC	Decolonization (previously categorized as IB, but mixed results as far as effectiveness and feasibility in neonates warrant a change in category)
II	Cohort patients (dedicated staff to care for colonized patients)
II	Education/training for all healthcare providers
II	Administrative and fiscal support
II	Communication system within hospital, community, nation, and global when indicated (reporting system). Report cases as per state regulations
II	Data collection (monitoring) and analysis—angiobiograms, trend recognition

Source: Adapted from Table 2 "Centers for Disease Control and Prevention/HICPAC MRSA Management" and Table 3 "Recommendations for Surveillance, Isolation, Cohorting, and Communication" in Newman, K. M. (2016). Surveillance and isolation of methicillin-resistant *Staphylococcus aureus* colonization in the neonatal intensive care unit. *Advances in Neonatal Care, 16*(4), 301, 303, 304. doi:10.1097/ANC.0000000000000312

CASE STUDY

Identification of the Problem. Baby Q is a 3,100 g 40-week gestation female infant whose mother resided in a country with known Zika virus-infected mosquitoes. She had a head circumference in the 3rd to 10th percentile but otherwise presented with a normal examination. She initially passed a routine hearing screen (otoacoustic emission), but per protocol for Zika-exposure was tested using an automated ABR screen which did not pass on the left ear.

Assessment: History and Physical Examination. The mother received the majority of her prenatal care in the Dominican Republic, then New Jersey during the last trimester. She transferred care to a practice in Rhode Island 2 weeks prior to delivery with incomplete obstetric records. She was a 20-year-old G3 P1 Hispanic woman. She reported a benign medical history. There was a verbal report of a negative Zika test, but no physical copy of the labwork. Her prenatal labwork included blood type A positive, antibody screen negative, rapid plasma reagin unknown (test sent on admission—non-reactive), rubella unknown (test sent—negative),

hepatitis B and C negative, HIV negative, and group B *Streptococcus* positive. She denied toxic habits. Her urine toxicology screen came back negative. Mother presented in labor with intact membranes and was delivered by repeat cesarean section. Membranes were ruptured artificially at delivery—fluid was clear. At delivery, infant was vigorous and required no resuscitation. APGAR scores were 8 at 1 minute and 9 at 5 minutes.

On admission, the infant's weight was 3,100 g (10th–25th percentile), length was 51 cm (25th–50th percentile), and head circumference was 33 cm (3rd–10th percentile). Vital signs were within normal limits. She was alert, active, with normal tone. She did not have obvious microcephaly or an abnormally shaped head. Her fontanels were open, soft, and flat. Sutures were mobile. Her eyes were in alignment with ears and normally shaped. Her nares were patent and palate intact. The neck was supple and without abnormal masses. Her clavicles were intact and without crepitus. The chest was symmetrical, breath sounds were clear and equal, and there were no retractions. She had a grade II/VI systolic murmur auscultated at the left sternal border which was resolved in 24 hours. Her femoral and peripheral pulses were 2+ equal. The abdomen was soft, non-tender, and without abnormal mass or organomegaly. She had normal female genitalia and a patent anus. Her hip examination was normal, and she had normal upper and lower extremities. There were normal grasp and suck and a symmetrical Moro response.

During her hospitalization, the infant was breastfeeding well, voiding, and stooling. She remained in the normal newborn nursery. She received hepatitis B vaccine. The infant passed the critical congenital heart disease screen. Discharge occurred on the fourth day of life.

■ Differential Diagnosis

- Hearing deficit of unknown origin
- Mechanical functions limiting passage of hearing screen (such as canal blockage with vernix, equipment failure)
- Zika virus infection with hearing loss

■ Diagnostic Tests

- Urine PCR for Zika
- Serum Zika IgM antibody capture enzyme-linked immunosorbent assay (MAC-ELISA)
- Serum Zika RNA
- Urine toxicology screen (sent for lack of maternal obstetric records)
- Newborn metabolic screen

Working Diagnosis. The urine PCR was positive for Zika. The serum Zika MAC-ELISA IgM was negative. However, Zika RNA was detected using the rRT-PCR Triaplex PCR assay. The working diagnosis was CZS as a possible cause of hearing deficit.

Development of Management Plan. Diagnosis of CZS required a multidisciplinary approach. A referral was made to audiology for a diagnostic brainstem auditory evoked response (BAER), with plans to involve an ear nose throat (ENT) specialist for potential hearing aids or cochlear implants if needed. A neurologist was consulted, and an MRI was ordered. A cardiologist was consulted, and an echocardiogram was ordered. The team requested a consult with an ophthalmologist, who performed an eye examination. A referral was made to early intervention. The private pediatrician was informed of all findings and recommended follow-up.

Implementation and Evaluation of Effectiveness. The MRI revealed normal anatomy with no evidence of microcephaly or abnormal development. The eye examination was normal. The echocardiogram showed normal anatomy and cardiac function. The pediatrician monitored for possible future development of microcephaly. By 3 months, the infant developed feeding difficulties, dusky episodes with feeding, noisy breathing, and stridor. A swallow study demonstrated dysphagia with coughing episodes triggered. The ENT specialist re-evaluated and found that the infant had laryngomalacia. Prevacid and Zantac were ordered for gastroesophageal reflux. Sleep apnea was also documented. Despite the feeding difficulties, at 14 months she weighed 11.3 kg (91st percentile), had a length of 83 cm (98th percentile), and had a head circumference of 45.6 cm (52nd percentile). This case demonstrated the subtle changes that can occur with CZS and need for ongoing monitoring and evaluation.

QUALITY ASSESSMENT AND QUALITY IMPROVEMENT ACTIVITY BOX

Situational Awareness of Emerging Infections in the Perinatal Population

Preparing for emerging infections:

In 2017, the American Academy of Pediatrics Committee on the Fetus and Newborn published a clinical report on disaster preparedness in the NICU (Barfield, Krug, AAP Committee on Fetus and Newborn, & AAP Disaster Preparedness Advisory Council, 2017). This report addressed possible natural and industrial disasters, including pandemic infectious disease and the possibility of a bioterrorist event. Pregnant women and infants are seen as particularly vulnerable to infectious outbreak or attack. This is due to alterations in immune function and lack of information in these populations. Some biologic agents (plague, smallpox, radioactive agents) target dividing cells, making infants particularly at risk (Barfield et al., 2017). Both this clinical report and the *Guidelines of Perinatal Care*, Eighth Edition (Kilpatrick, Papile, & Macones, 2017) provide a list of suggested online and continuously updated resources to be used in case of an infectious event that should be referenced in planning.

Each NICU, hospital, community, state, and region should develop a program for awareness of local infections and a plan for responses. While many hospitals have disaster plans that include memoranda of understanding for the care and transfer of adults, not all address pediatric patients (Barfield et al., 2017). This could have significant consequences in the event of a pandemic or bioterrorism event. Disaster plans should be local, collaborative, and require regular review and education. Table 26.6 includes a list of potential quality metrics and activities for use in disaster planning.

(*continued*)

QUALITY ASSESSMENT AND QUALITY IMPROVEMENT ACTIVITY BOX (*continued*)

TABLE 26.6

POTENTIAL QUALITY METRICS AND ACTIVITIES RELATED TO EMERGING INFECTIONS

Awareness and evaluation of risk	• Does maternal history taking include history of recent travel? • Does maternal history taking and care include screening for signs of infection? • Is there a mechanism for sharing maternal infectious risks with neonatal providers? • Does the NICU have a program for periodic review of local pathogens? • Is the unit compliant with CDC infection prevention guidelines such as handwashing audits? • Does the unit perform audits of isolation technique? Drills? • Are nursing and medical staff aware of local, national, and international guidelines and resources available to guide the evaluation, treatment, and prevention of spread of infectious disease?
Planning	• Does the institution/unit have a plan for emergency preparedness that includes an infectious pathogen plan? • Does the plan include care of the mother–infant dyad and for the provision of maternal breast milk whenever possible? • Is there budget to support supplies needed for emergency planning? • Is simulation available and used to prepare for emergency planning and isolation technique? • Does planning include collaboration with local and regional facilities in the event of large-scale evacuation?

References

Barfield, W. D., Krug, S. E., AAP Committee on Fetus and Newborn, & AAP Disaster Preparedness Advisory Council. (2017). Disaster preparedness in neonatal intensive care units. *Pediatrics, 139*(5), e20170507. doi:10.1542/peds.2017-0507

Kilpatrick, S. J., Papile, L.-A., & Macones, G. A. (Eds.). (2017). Perinatal Infections, *Guidelines for perinatal care* (8th ed., pp. 479–558). Elk Grove Village, IL: American Academy of Pediatrics and Washington, DC: The American College of Obstetricians and Gynecologists.

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ONLINE RESOURCES

Barfield, W.D., Krug, S.E., AAP Committee on Fetus and Newborn, & AAP Disaster Preparedness Advisory Council. (2017). Disaster preparedness in neonatal intensive care units. *Pediatrics, 139*(5), e20170507. doi:10.1542/peds.2017-0507

Centers for Disease Control and Prevention. (2018). *National notifiable conditions (historical)*. Retrieved from https://wwwn.cdc.gov/nndss/conditions/notifiable/2018

Centers for Disease Control and Prevention. (n.d.-a). Division of high-consequence pathogens and pathology. Retrieved from https://www.cdc.gov/ncezid/dhcpp

Centers for Disease Control and Prevention. (n.d.-b). Emerging infections program. Retrieved from https://www.cdc.gov/ncezid/dpei/eip/index.html

Centers for Disease Control and Prevention. (2017). Explore travel health with the CDC Yellow Book. Retrieved from https://wwwnc.cdc.gov/travel/page/yellowbook-home

Morof, D. F., & Carroll, D. (2017, June 13). Advising travelers with specific needs: Pregnant travelers. In G. W. Brunette (Ed.), *2018 yellow book* [Online]. Retrieved from https://wwwnc.cdc.gov/travel/yellowbook/2018/advising-travelers-with-specific-needs/pregnant-travelers

Pandemic and All-Hazards Preparedness Reauthorization 2013. Retrieved from https://www.phe.gov/Preparedness/legal/pahpa/Pages/pahpra.aspx

Shealy, K. R. (2017, June 12). International travel with infants & children: Travel & breastfeeding. In G. W. Brunette (Ed.), *2018 yellow book* [Online]. Retrieved from https://wwwnc.cdc.gov/travel/yellowbook/2018/international-travel-with-infants-children/travel-and-breastfeeding

World Health Organization. Retrieved from http://www.who.int/en

World Health Organization. (n.d.). *WHO report on global surveillance of epidemic-prone infectious diseases–Introduction.* Retrieved from http://www.who.int/csr/resources/publications/introduction/en/index4.html

Worldwide Database for Nosocomial Outbreaks. Retrieved from http://www.outbreak-database.com

REFERENCES

Abdel-Hady, H., Hawas, S., El-Daker, M., & El-Kady, R. (2008). Extended-spectrum β-lactamase producing *Klebsiella pneumoniae* in neonatal intensive care unit. *Journal of Perinatology, 28*, 685–690. doi:10.1038/jp.2008.73

Acosta-Reyes, J., Navarro, E., Herrera, M. J., Goenaga, E., Ospina, M. L., Parra, E., Mercado, . . . Baquero, H. (2017). Severe neurologic disorders in 2 fetuses with Zika virus infection, Columbia. *Emerging Infectious Diseases, 23*(6), 982–984. doi:10.3201/eid2306.161702#

Adebanjo, T., Godfred-Cato, S., Viens, L., Fischer, M., Staples, J. E., Kuhnert-Tallman, W., & Moore, C. A. (2017). Update: Interim guidance for the diagnosis, evaluation, and management of infants with possible congenital Zika virus infection–United States, October 2017. *Morbidity and Mortality Weekly Report, 66*(41), 1089–1099. doi:10.15585;mmwr.mm6641a1#

Aderinboye, O., & Syed, S. S. (2010). Congenital babesiosis in a four-week-old female infant. *The Pediatric Infectious Disease Journal, 29*(2), 188. doi:10.1097/INF.0b013e3181c3c971#

Alter, M. J., Margolis, H. S., Bell, B. P., Bice, S. D., Buffington, J., Chamberland, M., . . . Williams, I. A. (1998). Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. *MMWR Recommendations and Reports, 47*(RR19), 1–39. Retrieved from https://www.cdc.gov/mmwr/preview/mmwrhtml/00055154.htm

Akturk, H., Sutcu, M., Somer, A., Acar, M., Karapinar, B. A., Aydin, D., . . . Salman, N. (2016). Vancomycin-resistant enterococci colonization in a neonatal intensive care unit: Who will be infected? *The Journal of Maternal-Fetal and Neonatal Medicine, 29*(21), 3478–3482. doi:10.3109/14767058.2015.1132693#

Al-Tawfiq, J. A. (2006). Father-to-infant transmission of community-acquired methicillin-resistant *Staphylococcus aureus* in a neonatal intensive care unit. *Infection Control and Hospital Epidemiology, 27*(6), 636–637. doi:10.1086/505097

Andrews, T. M. (2003). Current concepts in antibiotic resistance. *Current Opinion in Otolaryngology & Head and Neck Surgery, 11*, 409–415. doi:10.1097/00020840-200312000-00001

Arias, C. A., Contreras, G. A., & Murray, B. E. (2010). Management of multidrug-resistant enterococcal infections. *Clinical Microbiology and Infectious Diseases, 16*, 555–562. doi:10.1111/j.1469-0691.2010.03214.x

Arias, C. A., & Murray, B. E. (2019). Mechanisms of antibiotic resistance in enterococci. In E. L. Baron (Ed.), *UpToDate*. Retrieved from https://www.uptodate.com/contents/mechanisms-of-antibiotic-resistance-in-enterococci

Ashkenas, J., Buchanan, L., Burgess, J., Fairfield, H., Grady, D., Keller, J., . . . Yourish, K. (2015, January 26). How many ebola patients have been treated outside of Africa? *The New York Times*. Retrieved from https://www.nytimes.com/interactive/2014/07/31/world/africa/ebola-virus-outbreak-qa.html?action=click&contentCollection Africa&module=RelatedCoverage&region=EndOfArticle&pgtype=article

Azarian, T., Maraqa, N. F., Cook, R. L., Johnson, J. A., Bailey, C., Wheeler, S., . . . Salemi, M. (2016). Genomic epidemiology of methicillin-resistant *Staphylococcus aureus* in a neonatal intensive care unit. *PLoS One, 11*(10), e0164397. doi:10.1371/journal.pone.0164397#

Bagattini, M., Crivaro, V., Di Popolo, A., Gentile, F., Scarcella, A., Triassi, M., . . . Zarrilli, R. (2006). Molecular epidemiology of extended-spectrum beta-lactamase (ESBL)-producing *Klebsiella pneumoniae* in the neonatal intensive care unit of a university hospital in Italy. *Journal of Antimicrobial Chemotherapy, 57*(5), 979–982. doi:10.1093/jac/dkl077

Baley, J. E., & Leonard, E. G. (2013). Infections in the neonate. In A. A. Fanaroff & J. M. Fanaroff (Eds.), *Klaus & Fanaroff's care of the high-risk neonate* (6th ed., pp. 346–367). Philadelphia, PA: Elsevier Saunders.

Behari, P., Englund, J., Alcasid, G., Garcia-Houchins, S., & Weber, S. G. (2004). Transmission of methicillin-resistant *Staphylococcus aureus* to preterm infants through breast milk. *Infection Control and Hospital Epidemiology, 25*(9), 778–780. doi:10.1086/502476

Beigi, R. H. (2017). Emerging infectious diseases in pregnancy. *Obstetrics & Gynecology, 129*(5), 896–906. doi:10.1097/AOG.0000000000001978

Bizzarro, M. J., & Gallagher, P. G. (2007). Antibiotic-resistant organisms in the neonatal intensive care unit. *Seminars in Perinatology, 31*, 26–32. doi:10.1053/j.semperi.2007.01.004#

Blanchard, A. C., Quach, C., & Autmizquine, J. (2015). Staphylococcal infections in infants: Updates and current challenges. *Clinics in Perinatology, 42*(1), 119–132. doi:10.1016/j.clp.2014.10.013#

Blaschke, A. J., Korgenski, E. K., Daly, J. D., LaFleur, B., Pavia, A. T., & Byington, C. L. (2009). Extended-spectrum β-lactamase-producing pathogens in a children's hospital: A 5-year experience. *American Journal of Infection Control, 37*(6), 435–441. doi:10.1016/j.ajic.2008.09.019#

Boszczowski, I., Nicoletti, C., Puccini, D. M. T., Pinheiro, M., Soares, R. E., Van Der Heijden, I. M., . . . Levin, A. S. (2005). Outbreak of extended spectrum β-lactamase-producing *Klebsiella pneumoniae* infection in a neonatal intensive care unit related to onychomycosis in a health care worker. *The Pediatric Infectious Disease Journal, 24*(7), 648–650. doi:10.1097/01.inf.0000168844.55898.8f

Bozzola, E., Quondamcarlo, A., Krzysztofiak, A., Lancella, L., Romano, M., & Tozzi, A. (2011). Re-emergence of measles in young infants. *The Pediatric Infectious Disease Journal, 30*(3), 271. doi:10.1097/INF.0b013e31820676e8

Brouqui, P. (2009). Facing highly infectious diseases: New trends and current concepts. *Clinical Microbiology and Infectious Diseases, 15*, 700–705. doi:10.1111/j.1469-0691.2009.02873.x

Burton, D. C., Edwards, J. R., Horan, T. C., Jernigan, J. A., & Fridkin, S. K. (2009). Methicillin-resistant *Staphylococcus aureus* central line-associated bloodstream infections in US intensive care units, 1997-2007. *Journal of the American Medical Association, 301*(7), 727–736. doi:10.1001/jama.2009.153

Butin, M., Martins-Simões, P., Rasigade, J.-P., Picaud, J.-C., & Laurent, F. (2017). Worldwide endemicity of a multidrug-resistant *Staphylococcus capitis* clone involved in neonatal sepsis. *Emerging Infectious Diseases, 23*(3), 538–539. doi:10.3201/eid2303.160833

Cantley, J. B., & Milstone, A. M. (2015). Bloodstream infections: Epidemiology and resistance. *Clinics in Perinatology, 42*(1), 1–16. doi:10.1016/j.clp.2014.10.002

Cantley, J. B., & Patel, S. J. (2014). Antimicrobial stewardship in the NICU. *Infectious Disease Clinics of North America, 28*(2), 247–261. doi:10.1016/j.idc.2014.01.005#

Carey, A. J., Della-Latta, P., Huard, R., Wu, F., Graham, P. L., Carp, D., & Saiman, L. (2010). Changes in the molecular epidemiological characteristics of methicillin-resistant *Staphylococcus aureus* in a neonatal intensive care unit. *Infection Control and Hospital Epidemiology, 31*(6), 613–619. doi:10.1086/652526#

Carey, A. J., Duchon, J., Della-Latta, P., & Saiman, L. (2010). The epidemiology of methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* in a neonatal intensive care unit, 2000-2007. *Journal of Perinatology, 30*(2), 135–139. doi:10.1038/jp.2009.119#

Carey, A. J., & Long, S. S. (2010). *Staphylococcus aureus*: A continuously evolving and formidable pathogen in the neonatal intensive care unit. *Clinics in Perinatology, 37*(3), 535–546. doi:10.1016/j.clp.2010.05.002

Castillo-Salgado, C. (2010). Trends and directions of global public health surveillance. *Epidemiologic Reviews, 32*, 93–109. doi:10.1093/epirev/mxq008#

Cavalcanti, M. G., Cabral-Castro, M. J., Gonçalves, J. L. S., Santana, L. S., Pimenta, E. S., & Peralta, J. M. (2017). Zika virus shedding in human milk during lactation: An unlikely source of infection? *International Journal of Infectious Diseases, 57*, 70–72. doi:10.1016/j.ijid.2017.01.042

Centers for Disease Control and Prevention. (2008). *Haemophilus influenza* serotype b (HIB). Retrieved from https://www.cdc.gov/hi-disease/clinicians.html

Chiu, C.-H., Michelow, I. C., Cronin, J., Ringer, S. A., Ferris, T. G., & Puopolo, K. M. (2011). Effectiveness of a guideline to reduce vancomycin use in the neonatal intensive care unit. *The Pediatric Infectious Disease Journal, 30*(4), 273–278. doi:10.1097/INF.0b013e3182011d12#

Chua, A., Prat, I., Nuebling, C. M., Wood, D., & Moussy, F. (2017). Update on Zika diagnostic tests and WHO's related activities. *PLoS Neglected Tropical Diseases, 11*(2), e0005269. doi:10.1371/journal.pntd.0005269#

Chuang, Y.-Y., Huang, Y.-C., Lee, C.-Y., Lin, T.-Y., Lien, R., & Chou, Y.-H. (2004). Methicillin-resistant *Staphylococcus aureus* bacteraemia in neonatal intensive care units: An analysis of 90 episodes. *Acta Paediatrica, 93*, 786–790. doi:10.1080/08035250410028084#

Climo, M. W., Yokoe, D. S., Warren, D. K., Perl, T. M., Bolon, M., Herwaldt, L. A., . . . Wong, E. S. (2013). Effect of daily chlorhexidine bathing on hospital-acquired infection. *New England Journal of Medicine, 368*(6), 533–542. doi:10.1056/NEJMoa1113849

Coelho, A. V. C., & Crovella, S. (2017). Microcephaly prevalence in infants born to Zika virus-infected women: A systematic review and meta-analysis. *International Journal of Molecular Science, 18*(8), 1714. doi:10.3390/ijms18081714#

Collignon, P., Powers, J. H., Chiller, T. M., Aidara-Kane, A., & Aarestrup, F. M. (2009). World Health Organization ranking of antimicrobials according to their importance in human medicine: A critical step for developing risk management strategies for the use of antimicrobials in food production animals. *Clinical Infectious Diseases, 49*(1), 132–141. doi:10.1086/599374#

Colt, S., Garcia-Casal, M. N., Pena-Rosas, J. P., Finkelstein, J. L., Rayco-Solon, P., Weise Prinzo, Z. C., & Mehta, S. (2017). Transmission of Zika virus through breast milk and other breastfeeding-related bodily-fluids: A systemic review. *PLoS Neglected Tropical Diseases, 11*(4), e0005528. doi:10.1371/journal.pntd.0005528

Committee on Infectious Diseases American Academy of Pediatrics. (2015a). Antimicrobial resistance and antimicrobial stewardship: Appropriate and judicious use of antimicrobial agents. In D. W. Kimberlin, M. T. Brady, M. A. Jackson, & S. S. Long (Eds.), *Red Book: 2015 Report of the Committee on Infectious Diseases* (30th ed., pp. 874–880). Elk Grove Village, IL: American Academy of Pediatrics.

Committee on Infectious Diseases American Academy of Pediatrics. (2015b). Measles. In D. W. Kimberlin, M. T. Brady, M. A. Jackson, & S. S. Long (Eds.), *Red book: 2015 Report of the Committee on Infectious Diseases* (30th ed., pp. 535–547). Elk Grove Village, IL: American Academy of Pediatrics.

Conte, M. P., Venditti, M., Chiarini, F., D'Ettore, G., Zamboni, I., Scoarughi, G. L., . . . Orsi, G. B. (2005). Extended spectrum beta-lactamase-producing *Klebsiella pneumoniae* outbreaks during a third generation cephalosporin restriction policy. *Journal of Chemotherapy, 17*(1), 66–73. doi:10.1179/joc.2005.17.1.66

Cotten, C. M. (2016). Adverse consequences of neonatal antibiotic exposure. *Current Opinions in Pediatrics, 28*(2), 141–149. doi:10.1097/MOP.0000000000000338#

Cragan, J. D., Mai, C. T., Petersen, E. E., Liberman, R. F., Forestieri, N. E., Stevens, A. C., . . . Honein, M. A. (2017). Baseline prevalence of birth defects associated with congenital Zika virus infection–Massachusetts, North Carolina, and Atlanta, Georgia, 2013-2014. *Morbidity and Mortality Weekly Report, 66*(8), 219–222. doi:10.15585/mmwr.mm6608a4#

Crivaro, V., Bagattini, M., Salza, M. F., Raimondi, F., Rossano, F., Triassi, M., & Zarrilli, R. (2007). Risk factors for extended-spectrum β-lactamase-producing *Serratia marcescens* and *Klebsiella pneumoniae* acquisition in a neonatal intensive care unit. *Journal of Hospital Infection, 67*, 135–141. doi:10.1016/j.jhin.2007.07.026#

D'Angelo, D. V., von Essen, B. S., Lamias, M. J., Shulman, H., Hernandez-Virella, W. I., Taraporewalla, A. J., . . . Warner, L. (2017). Measures taken to prevent Zika virus infection during pregnancy–Puerto Rico, 2016. *Morbidity and Mortality Weekly Report, 66*(22), 574–578. doi:10.15585/mmwr.mm6622a2#

DeLisle, S., & Perl, T. M. (2003). Vancomycin-resistant enterococci: A road map on how to prevent the emergence and transmission of antimicrobial resistance. *Chest, 123*(5 Suppl.), 504S–518S. doi:10.1378/chest.123.5_suppl.504S

Desai, S. K., Hartman, S. D., Jayarajan, S., Liu, S., & Gallicano, G. I. (2017). Zika virus (ZIKV): A review of proposed mechanisms of transmission and associated congenital abnormalities. *American Journal of Stem Cells, 6*(2), 13–22. Retrieved from http://www.ajsc.us/files/ajsc0057560.pdf

Di Cavalcanti, D., Alves, L. V., Furtado, G. J., Santos, C. C., Feitosa, F. G., Ribeiro, M. C., . . . Alves, J. G. (2017). Echocardiographic findings in infants with presumed congenital Zika syndrome: Retrospective case series study. *PLoS One, 12*(4), e0175065. doi:10.1371/journal.pone.0175065#

Di Pentima, M. C., & Chan, S. (2010). Impact of antimicrobial stewardship program on vancomycin use in a pediatric teaching hospital. *The Pediatric Infectious Disease Journal, 29*(8), 707–711. doi:10.1097/INF.0b013e3181d683f8#

Dolapo, O., Dhanireddy, R., & Talati, A. J. (2014). Trends of *Staphylococcus aureus* bloodstream infections in a neonatal intensive care unit from 2000-2009. *BMC Pediatrics, 14*, 121. doi:10.1186/1471-2431-14-121#

Doyle, J. S., Buising, K. L., Thursky, K. A., Worth, L. J., & Richards, M. J. (2011). Epidemiology of infections acquired in intensive care units. *Seminars in Respiratory and Critical Care Medicine, 32*(2), 115–138. doi:10.1055/s-0031-1275525

Enomoto, M., Morioka, I., Morisawa, T., Yokoyama, N., & Matsuo, M. (2009). A novel tool for detecting neonatal infections using multiplex polymerase chain reaction. *Neonatology, 96*(2), 102–108. doi:10.1159/000208791#

Eppes, C., Rac, M., Dunn, J., Versalovic, J., Murray, K. O., Suter, M. A., . . . Aagaard, K. M. (2017). Testing for Zika virus infection in pregnancy: Key concepts to deal with an emerging epidemic. *American Journal of Obstetrics and Gynecology, 216*(3), 209–225. doi:10.1016/j.ajog.2017.01.020

Faizan, M. I., Abdullah, M., Ali, S., Naqvi, I. H., Ahmed, A., & Parveen, S. (2016). Zika virus-induced microcephaly and its possible molecular mechanism. *Intervirology, 59*, 152–158. doi:10.1159/000452950#

Fishman, N. (2006). Antimicrobial stewardship. *American Journal of Infection Control, 34*, S55–S63. doi:10.1016/j.ajic.2006.05.237#

Flaherty, G. F., Moran, B., & Higgins, P. (2017). International travel and blood donation: Risks and restrictions. *Travel Medicine, 24*(3). doi:10.1093/jtm/tax004

Food and Drug Administration. (2018, March 6). FDA approves first tests to screen for tickborne parasite in whole blood and plasma to protect the U.S. blood supply. *FDA News Release*. Retrieved from https://www.fda.gov/news-events/press-announcements/fda-approves-first-tests-screen-tickborne-parasite-whole-blood-and-plasma-protect-us-blood-supply

Fox, L. M., Wingerter, S., Ahmed, A., Arnold, A., Chou, J., Rhein, L., & Levy, O. (2006). Neonatal babesiosis: Case report and review of the literature. *The Pediatric Infectious Disease Journal, 25*(2), 169–173. doi:10.1097/01.inf.0000195438.09628.b0#

Francis, S. T., Rawal, S., Roberts, H., Riley, P., Planche, T., & Kennea, N. L. (2010). Detection of methicillin-resistant *Staphylococcus aureus* (MRSA) colonization in newborn infants using real-time polymerase chain reaction (PCR). *Acta Paediatrica, 99*, 1691–1694. doi:10.1111/j.1651-2227.2010.01899x

Garland, J. S., Alex, C. P., Sevallius, J. M., Murphy, D. M., Good, M. J., Volberding, A. M., . . . Maki, D. G. (2008). Cohort study of the pathogenesis and molecular epidemiology of catheter-related bloodstream infection in neonates with peripherally inserted central venous catheters. *Infection Control and Hospital Epidemiology, 29*(3), 243–249. doi:10.1086/526439#

Gerber, S. I., Jones, R. C., Scott, M. V., Price, J. S., Dworkin, M. S., Filipell, M. B., . . . Noskin, G. A. (2006). Management of outbreaks of methicillin-resistant *Staphylococcus aureus* infection in the neonatal intensive care unit: A consensus statement. *Infection Control and Hospital Epidemiology, 27*(2), 139–145. doi:10.1086/501216

Germain, M., & Goldman, M. (2002). Blood donor selection and screening: Strategies to reduce recipient risk. *American Journal of Therapeutics, 9*(5), 406–410. doi:10.1097/00045391-200209000-00007

Giuffrè, M., Geraci, D. M., Bonura, C., Saporito, L., Graziano, G., Insinga, V., . . . Mammina, C. (2016). The increasing challenge of multidrug-resistant gram-negative bacilli: Results of a 5-year active surveillance program in a neonatal intensive care unit. *Medicine (Baltimore), 95*(10), e3016. doi:10.1097/MD.0000000000003016

Gould, E. (2009). Emerging viruses and the significance of climate change. *Clinics in Microbiology and Infections, 15*(6), 503. doi:10.1111/j.1469-0691.2009.02845.x

Graham, J., Stockley, K., & Goldman, R. D. (2011). Tick-borne illnesses: A CME update. *Pediatric Emergency Care, 27*(2), 141–147. doi:10.1097/PEC.0b013e318209f0b3#

Grant, P. S., Charns, L. G., Rawot, B. W., & Benedetti, S. G. (2008). Consideration to culture health care workers related to increased methicillin-resistant *Staphylococcus aureus* activity in a neonatal intensive care unit. *American Journal Infection Control, 36*(9), 638–643. doi:10.1016/j.ajic.2008.03.006#

Greenfield, R. A., & Bronze, M. S. (2010). Emerging pathogens and knowledge in infectious diseases. *The American Journal of the Medical Sciences, 340*(3), 177–180. doi:10.1097/maj.0b013e3181e937fe

Gregory, K. E. (2016). A brief history of antibiotics in the neonatal intensive care unit: From routine prophylaxis to antimicrobial stewardship. *The Journal of Perinatal & Neonatal Nursing, 30*(2), 88–92. doi:10.1097/JPN.0000000000000174#

Gregory. M. L., Eichenwald, E. C., & Puopolo, K. M. (2009). Seven-year experience with a surveillance program to reduce methicillin-resistant

Staphylococcus aureus colonization in a neonatal intensive care unit. *Pediatrics, 123*, e790–e796. doi:10.1542/peds.2008-1526#

Gundes, S., Arisoy, A. E., Kolayli, F., Karaali, E., Turker, G., Sanic, A., . . . Vahaboglu, H. (2005). An outbreak of SHV-5 producing *Klebsiella pneumoniae* in a neonatal intensive care unit; meropenem failed to avoid fecal colonization. *The New Microbiologica, 28*(3), 231–236.

Hammer, B. M., Lardieri, A. B., & Morgan, J. A. (2016). Appropriate use of vancomycin in NICU despite free-for-all policy. *The Journal of Pediatric Pharmacology and Therapeutics, 21*(3), 207–212. doi:10.5863/1551-6776-21.3.207#

Hart, A. M. (2011). Practice antibiotic stewardship to preserve benefits. *The Clinical Advisor, 14*, 45–55. Retrieved from https://www.clinicaladvisor.com/home/features/practice-antibiotic-stewardship-to-preserve-benefits/2/

Hawes, J. A., & Lee, K.-S. (2018). Reduction in central line-associated bloodstream infections in a NICU: Practical lessons for its achievement and sustainability. *Neonatal Network, 37*(2), 105–115. doi:10.1891/0730-0832.37.2.105

Healy, C. M., Hulten, K. G., Palazzi, D. L., Campbell, J. R., & Baker, C. J. (2004). Emergence of new strains of methicillin-resistant *Staphylococcus aureus* in a neonatal intensive care unit. *Clinical Infectious Diseases, 39*(10), 1460–1466. doi:10.1086/425321

Heinrich, N., Mueller, A., Bartmann, P., Simon, A., Bierbaum, G., & Engelhart, S. (2011). Successful management of an MRSA outbreak in a neonatal intensive care unit. *European Journal of Clinical Microbiology & Infectious Diseases, 30*(7), 909–913. doi:10.1007/s10096-011-1175-4#

Herwaldt, B. L., Linden, J. V., Bosserman, E., Young, C., Olkowska, D., & Wilson, M. (2011). Transfusion-associated babesiosis in the United States: A description of cases. *Annals of Internal Medicine, 155*(8), 509–519. doi:10.1097/INF.0b013e3182370b95

Higgins, R. D., Baker, C. J., & Raju, T. N. K. (2010). Executive summary of the workshop on infection in the high risk neonate. *Journal of Perinatology, 30*(6), 379–383. doi:10.1038/jp.2009.199#

Hocevar, S. N., Lessa, F. C., Gallagher, L., Conover, C., Gorwitz, R., & Iwamoto, M. (2014). Infection prevention practices in neonatal intensive care units reporting to the National Healthcare Safety Network. *Infection Control & Hospital Epidemiology, 35*(9), 1126–1132. doi:10.1086/677636#

Hoffman, M. (2018). FDA approves duo of *Babesia microti* tests for human blood, plasma. *MD Magazine*. Retrieved from https://www.mdmag.com/medical-news/fda-approves-duo-of-babesia

Hopkins, D. (Ed.). (2007). *World health report: A safer future*. Geneva, Switzerland: World Health Organization.

Huang, Y.-C., Lien, R.-I., Su, L.-H., Chou, Y.-H., & Lin, T.-Y. (2011). Successful control of methicillin-resistant *Staphylococcus aureus* in endemic neonatal intensive care units–A 7-year campaign. *PLoS One, 6*(8), e23001. doi:10.1371/journal.pone.0023001#

Huang, Y.-C., Zhuang, S., & Du, M. (2007). Risk factors of nosocomial infection with extended-spectrum beta-lactamase-producing bacteria in a neonatal intensive care unit in China. *Infection, 35*(5), 339–345. doi:10.1007/s15010-007-6356-9

Hyuang, Y.-C., Chou, Y.-H., Su, L.-H., Lien, R.-I., & Lin, T.-Y. (2006). Methicillin-resistant *Staphylococcus aureus* colonization and its association with infection among infants hospitalized in neonatal intensive care units. *Pediatrics, 118*(2), 469-474. doi:10.1542/peds.2006-0254

Iregbu, K. C., & Anwaal, U. (2007). Extended-spectrum beta-lactamase-producing *Klebsiella pneumoniae* septicaemia outbreak in the neonatal intensive care unit of a tertiary hospital in Nigeria. *African Journal of Medicine and Medical Sciences, 36*(3), 225–228.

Jaenisch, T., Rosenberger, K. D., Brito, C., Brady, O., Brasil, P., & Marques, E. T. A. (2017). Risk of microcephaly after Zika virus infection in Brazil, 2015 to 2016. *Bulletin of the World Health Organization, 95*(3), 191–198. doi:10.2471/BLT.16.178608#

Jain, A., Agarwal, J., & Bansal, S. (2004). Prevalence of methicillin-resistant, coagulase-negative staphylococci in neonatal intensive care units: Findings from a tertiary care hospital in India. *Journal of Medical Microbiology, 53*, 941–944. doi:10.1099/jmm.0.45565-0#

Jain, A., Roy, I., Gupta, M. K., Kumar, M., & Agarwal, S. K. (2003). Prevalence of extended-spectrum β-lactamase-producing gram-negative bacteria in septicaemic neonates in a tertiary care hospital. *Journal of Medical Microbiology, 52*(5), 421–425. doi:10.1099/jmm.0.04966-0#

Jamieson, D. J., Honein, M. A., Rasmussen, S. A., Williams, J. L., Swedlow, D. L., Biggerstaff, M. S., . . . Novel Influenza A (H1N1) Pregnancy Working Group. (2009). H1N1 2009 influenza virus infection during pregnancy in the USA. *Lancet, 374*(9688), 451–458. doi:10.1016/S0140-6736(09)61304-0

Janssens, S., Schotsaert, M., Karnik, R., Balasubramaniam, V., Dejosez, M., Meissner, A., . . . Zwaka, T. P. (2018). Zika virus alters DNA methylation of neural genes in an organoid model of the developing human brain. *mSystems, 3*(1), e00219-17. doi:10.1128/mSystems.00219-17

Johnson, P. J. (2012). Antibiotic resistance in the NICU. *Neonatal Network, 31*(2), 109–114. doi:10.1891/0730-0832.31.2.109

Kamath, S., Mallaya, S., & Shenoy, S. (2010). Nosocomial infections in neonatal intensive care units: Profile, risk factor assessment and antibiogram. *Indian Journal of Pediatrics, 77*(1), 37–39. doi:10.1007/s12098-010-0005-5

Kanj, S. S., & Kanafani, Z. A. (2011). Current concepts in antimicrobial therapy against resistant gram-negative organisms: Extended-spectrum β-lactamase-producing enterobacteriaceae, carbapenem-resistant enterobacteriaceae, and multidrug-resistant *Pseudomonas aeruginosa*. *Mayo Clinic Proceedings, 86*(3), 250–259. doi:10.4065/mcp.2010.0674

Kaushik, A., Kest, H., Zauk, A., DeBari, V. A., & Lamacchia, M. (2015). Impact of routine methicillin-resistant *Staphylococcus aureus* (MRSA) surveillance and cohorting on MRSA-related bloodstream infection in neonatal intensive care unit. *American Journal of Perinatology, 32*, 531–536. doi:10.1055/s-0034-1395481#

Kourtis, A. P., Read, J. S., & Jamieson, D. J. (2014). Pregnancy and infection. *New England Journal of Medicine, 370*(23), 2211–2218. doi:10.1056/NEJMra1213566#

Kristóf, K., Szabo, D., March, J. W., Cser, V., Janik, L., Rozgonyi, F., . . . Paterson, D. L. (2007). Extended-spectrum beta-lactamase-producing *Klebsiella* spp. in a neonatal intensive care unit: Risk factors for the infection and the dynamics of the molecular epidemiology. *European Journal of Clinical Microbiology and Infectious Disease, 26*, 563–570. doi:10.1007/s10096-007-0338-9#

Lagunas-Rangel, F. A., Viveros-Sandoval, M. E., & Reyes-Sandoval, A. (2017). Current trends in Zika vaccine development. *Journal of Virus Eradication, 3*(3), 124–127. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5518240

Leal, M. C., Muniz, L. F., Caldas Neto, S. S., van der Linden, V., & Ramos, R. C. F. (2016). Sensorineural hearing loss in a case of congenital Zika virus. *Brazilian Journal of Otolaryngology*. doi:10.1016/j.bjorl.2016.06.001

Leal, M. C., Muniz, L. F., Ferreira, T. S. A., Santos, C. M., Almeida, L. C., van der Linden, V., . . . Neto, S. S. C. (2016). Hearing loss in infants with microcephaly and evidence of congenital Zika virus infection–Brazil, November 2015–May 2016. *Morbidity and Mortality Weekly Report, 65*(34), 917–919. doi:10.15585/mmwr.mm6534e3

Lee, J., Pai, H., Kim, Y. K., Kim, N. H., Eun, B. W., Kang, H. J., . . . Ahn, H. S. (2007). Control of extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae* in a children's hospital by changing antimicrobial agent usage policy. *Journal of Antimicrobial Chemotherapy, 60*(3), 629–637. doi:10.1093/jac/dkm225

Lepelletier, D., Corvec, S., Caillon, J., Reynaud, A., Rozé, J.-C., & Gras-Leguen, C. (2009). Eradication of methicillin-resistant *staphylococcus aureus* in a neonatal intensive care unit: Which measures for which success? *American Journal of Infection Control, 37*(3), 195–200. doi:10.1016/j.ajic.2008.09.024#

Lessa, F. C., Edwards, J. R., Fridkin, S. K., Tenover, F. C., Horan, T. C., & Gorwitz, R. J. (2009). Trends in incidence of late-onset methicillin-resistant *Staphylococcus aureus* infection in neonatal intensive care units: Data from the National Nosocomial Infections Surveillance System, 1995-2004. *The Pediatric Infectious Disease Journal, 28*(7), 577–581. doi:10.1097/INF.0b013e31819988bf

Levin, A. E., & Krause, P. J. (2016). Transfusion-transmitted babesiosis: Is it time to screen the blood supply? *Current Opinions in Hematology, 23*(6), 573–580. doi:10.1097/MOH.0000000000000287

Lipsett, P. A. (2008). Antimicrobial stewardship in the ICU. *Contemporary Critical Care, 6*(5), 1–12.

López-Cerero, L., De Cueto, M., Saenz, C., Navarro, D., Velasco, C., Rodriguez-Baño, J., & Pascual, A. (2008). Neonatal sepsis caused by a CTX-M-32-producing *Escherichia coli* isolate. *Journal of Medical Microbiology, 57*(10), 1303–1305. doi:10.1099/jmm.0.2008/000729-0

Louie, T. (2011). Antimicrobial Stewardship: A review. *Infectious Diseases in Clinical Practice, 19*(6), 382–387. doi:10.1097/IPC.0b013e3182349ca5

Lowy, F. D. (2019). Methicillin-resistant *Staphylococcus aureus* (MRSA): Microbiology. In E. L. Baron (Ed.), *UpToDate*. Retrieved from https://www.uptodate.com/contents/methicillin-resistant-staphylococcus-aureus-mrsa-microbiology

Mammina, C., Di Carlo, P., Cipolla, D., Giuffrè, M., Cassucio, A., Di Gaetano, V., . . . Corsello, G. (2007). Surveillance of multidrug-resistant gram-negative bacilli in a neonatal intensive care unit: Prominent role of cross transmission. *American Journal of Infection Control, 35*(4), 222–230. doi:10.1016/j.ajic.2006.04.210

Maragakis, L. L. (2010). Recognition and prevention of multidrug-resistant gram-negative bacteria in the intensive care unit. *Critical Care Medicine, 38S*, S345–S351. doi:10.1097/CCM.0b013e3181e6cbc5

Maraqa, N. F., Aigbivbalu, L., Masnia-Iusan, C., Wludyka, P., Shareef, Z., Bailey, C., & Rathore, M. H. (2011). Prevalence of and risk factors for methicillin-resistant *Staphylococcus aureus* colonization and infection among infants at a Level III neonatal intensive care unit. *American Journal of Infection Control, 39*(1), 35–41. doi:10.1016/j.ajic.2010.07.013#

Marrs, C., Olson, G., Saade, G., Hankins, G., Wen, T., Patel, J., & Weaver, S. (2016). Zika virus. and pregnancy: A review of the literature and clinical considerations. *American Journal of Perinatology, 33*(7), 625–639. doi:10.1055/s-0036-1580089#

Mattar, S., Ojeda, C., Arboleda, J., Arrieta, G., Bosch, I., Botia, I., . . . Montero, G. (2017). Case report: Microcephaly associated with Zika virus infection. *BMC Infectious Diseases, 17*, 423. doi:10.1186/s12879-017-2522-6

McArthur, M. A. (2017). Zika virus: Recent advances towards the development of vaccines and therapeutics. *Viruses, 9*(6), 143. doi:10.3390/v9060143#

McPherson, C., Liviskie, C., Zeller, B., Nelson, M. P., & Newland, J. G. (2018). Antimicrobial stewardship in neonates: Challenges and opportunities. *Neonatal Network, 37*(2), 116–123. doi:10.1891/0730-0832.37.2.116

Mesa, R. J., Blanc, V., Blanch, A. R., Cortes, P., Gonzalez, J. J., Lavilla, S., . . . Navarro, F. (2006). Extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae* in different environments (humans, food, animal farms and sewage). *Journal of Antimicrobial Chemotherapy, 58*(1), 211–215. doi:10.1093/jac/dkl211

Milstone, A. M., Budd, A., Shepard, J. W., Ross, T., Aucott, S., Carroll, K. C., & Perl, T. M. (2010). Role of decolonization in a comprehensive strategy to reduce methicillin-resistant *Staphylococcus aureus* infections in the neonatal intensive care unit: An observational cohort. *Infection Control and Hospital Epidemiology, 31*(5), 558–560. doi:10.1086/652449#

Milstone, A. M., Song, X., Coffin, S., & Elward, A. (2010). Identification and eradication of methicillin-resistant *Staphylococcus aureus* colonization in the neonatal intensive care unit: Results of a national survey. *Infection Control and Hospital Epidemiology, 31*(7), 766–768. doi:10.1086/653615

Mittal, R., Nguyen, D., Debs, L. H., Patel, A. P., Liu, G., Jhaveri, V. M., . . . Liu, X. Z. (2017). Zika virus: An emerging global health threat. *Frontiers in Cellular and Infection Microbiology, 7*, 486. doi:10.3389/fcimb.2017.00486#

Mohsen, L., Ramy, N., Saied, D., Akmal, D., Salama, N., Haleim, M. M. A., & Aly, H. (2017). Emerging antimicrobial resistance in early and late-onset neonatal sepsis. *Antimicrobial Resistance & Infection Control, 6*, 63. doi:10.1186/s13756-017-0225-9#

Mongkolrattanothai, K., Mankin, P., Cranston, J. B., & Gray, B. M. (2010). Molecular surveillance of *Staphylococcus aureus* colonization in a neonatal intensive care unit. *American Journal of Infection Control, 38*(8), 660–663. doi:10.1016/j.ajic.2010.01.014#

Morgan, D., Kirkbride, H., Hewitt, K., Said, B., & Walsh, A. L. (2009). Assessing the risk from emerging infections. *Epidemiology and Infection, 137*, 1521–1530. doi:10.1017/S0950268809990227#

Mosby, L., Rasmussen, S. A., & Jamieson, D. J. (2011, July). 2009 pandemic influenza A (H1N1) in pregnancy: A systematic review of the literature. *American Journal of Obstetrics and Gynecology, 205*, 10–18. doi:10.1016/j.ajog.2010.12.033#

Mulvey, M. R., & Simor, A. E. (2009). Antimicrobial resistance in hospitals: How concerned should we be? *Canadian Medical Association Journal, 180*(4), 408–415. doi:10.1503/cmaj.080239#

Murillo, J. L., Cohen, M., & Kreiswirth, B. (2010). Results of nasal screening for methicillin-resistant *Staphylococcus aureus* during a neonatal intensive care unit outbreak. *American Journal of Perinatology, 27*, 79–82. doi:10.1055/s-0029-1225531

Murki, S., Jonnala, S., Mohammed, F., & Reddy, A. (2010). Restriction of cephalosporins and control of extended spectrum β-lactamase producing gram negative bacteria in a neonatal intensive care unit. *Indian Pediatrics, 47*, 785–788. doi:10.1007/s13312-010-0118-y

Musso, D., Nhan, J., Robin, E., Roch, C., Bierlaire, D., Zisou, K., . . . Broult, J. (2014). Potential for Zika virus transmission through blood transfusion demonstrated during an outbreak in French Polynesia, November 2013 to February 2014. *Eurosurveillance, 19*(14), p.ii:20761.

Nambiar, S., Herwaldt, L. A., & Singh, N. (2003). Outbreak of invasive disease caused by methicillin-resistant *Staphylococcus aureus* in neonates and prevalence in the neonatal intensive care unit. *Pediatric Critical Care Medicine, 4*(2), 220–226. doi:10.1097/01.PCC.0000059736.20597.75#

Nelson, M. U., Bizzarro, M. J., Dembry, L. M., Baltimore, R. S., & Gallagher, P. G. (2014). One size does not fit all: Why universal decolonization strategies to prevent methicillin-resistant *Staphylococcus aureus* colonization and infection in adult intensive care units may be inappropriate for neonatal intensive care units. *Journal of Perinatology, 34*(9), 653–655. doi:10.1038/jp.2014.125#

Nelson, M. U., & Gallagher, P. G. (2012). Methicillin-resistant *Staphylococcus aureus* in the neonatal intensive care unit. *Seminars in Perinatology, 36*(6), 424–430. doi:10.1053/j.sempiri.2012.06.004#

Newland, J. G., & Hersh, A. L. (2010). Purpose and design of antimicrobial stewardship programs in pediatrics. *The Pediatric Infectious Disease Journal, 29*(9), 862–863. doi:10.1097/INF.0b013e3181ef2507#

Newman, K. M. (2016). Surveillance and isolation of methicillin-resistant *Staphylococcus aureus* colonization in the neonatal intensive care unit. *Advances in Neonatal Care, 16*(4), 298–307. doi:10.1097/ANC.0000000000000312#

Nguyen, S. M., Antony, K. M., Dudley, D. M., Kohn, S., Simmons, H. A., . . . Golos, T. G. (2017). Highly efficient maternal-fetal Zika virus transmission in pregnant rhesus macaques. *PLoS Pathogens, 13*(5), e1006378. doi:10.1371/journal.ppat.1006378#

Nunes, M. L., Carlini, C. R., Marinowic, D., Neto, F. K., Fiori, H. H., . . . da Costa, J. C. (2016). Microcephaly and Zika virus: A clinical and epidemiological analysis of the current outbreak in Brazil. *Jornal de Pediatria, 92*, 230–240. doi:10.1016/j.jped.2016.02.009

O'Connor, C., Philip, R. K., Kelleher, J., Powell, J., O'Gorman, A., Slevin, B., . . . Dunne, C. P. (2017). The first occurrence of a CTX-M ESBL-producing *Escherichia coli* outbreak mediated by mother to neonate transmission in an Irish neonatal intensive care unit. *BMC Infectious Diseases, 17*, 16. doi:10.1186/s12879-016-2142-6

Ofek-Shlomai, N., Benenson, S., Ergaz, Z., Peleg, O., Braunstein, R., & Bar-Oz, B. (2011). Gastrointestinal colonization with ESBL-producing *Klebsiella* in preterm babies–Is vancomycin to blame? *European*

Journal of Clinical Microbiology & Infectious Diseases, 31(4), 567–570. doi:10.1007/s10096-011-1348-1#

Otman, J., Cavassin, E. D., Perugini, M. E., & Vidotto, M. C. (2002). An outbreak of extended-spectrum β-lactamase-producing *Klebsiella* species in a neonatal intensive care unit in Brazil. *Infection Control and Hospital Epidemiology, 23*(1), 8–9. doi:10.1086/503447

Oussayef, N. L., Pillai, S. K., Honein, M. A., Beard, C. B., Bell, B., Boyle, C. A., . . . Jamieson, D. J. (2017). Zika virus–10 public health achievements in 2016 and future priorities. *Morbidity and Mortality Weekly Report, 65*(52), 1482–1488. doi:10.15585/mmwr.mm6552e1

Park, C.-H., Seo, J.-H., Lim, J.-Y., Woo, H.-O., & Youn, H. S. (2007). Changing trend of neonatal infection: Experience at a newly established regional medical center in Korea. *Pediatrics International, 49*, 24–30. doi:10.1111/j.1442-200x.2007.02310.x

Passi, D., Sharma, S., Dutta, S. R., & Ahmed, M. (2017). Zika virus diseases—The new face of an ancient enemy as global public health emergency (2016): Brief review and recent updates. *International Journal of Preventive Medicine, 8*, 6. doi:10.4103/2008-7802.199641#

Patel, S. J., Oshodi, A., Prasad, P., Delamora, P., Larson, E., Zaoutis, T., Paul, D.A., & Saiman, L. (2009). Antibiotic use in neonatal intensive care units and adherence with Centers for Disease Control and Prevention 12 step campaign to prevent antimicrobial resistance. *The Pediatric Infectious Disease Journal, 28*(12), 1047–1051. doi:10.1097/INF.0b013e3181b12484

Patel, S. J., Rosen, E., Zaoutis, T., Prasad, P., & Saiman, L. (2010). Neonatologists' perceptions of antimicrobial resistance and stewardship in neonatal intensive care units. *Infection Control and Hospital Epidemiology, 31*(12), 1298–1299. doi:10.1086/657334

Patel, S. J., & Saiman, L. (2010). Antibiotic resistance in NICU pathogens: Mechanisms, clinical impact, and prevention including antibiotic stewardship. *Clinics in Perinatology, 37*(3), 547–563. doi:10.1016/j.clp.2010.06.004#

Perlman, S. E., Saiman, L., & Larson, E. L. (2007). Risk factors for late-onset health care-associated bloodstream infections in patients in neonatal intensive care units. *American Journal of Infection Control, 35*(3), 177–182. doi:10.1016/j.ajic.2006.01.002#

Pessoa, A., van der Linden, V., Yeargin-Allsopp, M., Carvalho, M. D. C. G., Ribeiro, E. M., VanNaarden Braun, K., . . . Moore, C. A. (2018). Motor abnormalities and epilepsy in infants and children with evidence of congenital Zika virus infection. *Pediatrics, 141*(Suppl. 2), S167–S179. doi:10.1542/peds.2017-2038f

Pessoa-Silva, C. L., Moreira, B. M., Almeida, V. C., Flannery, B., Lins, M. C. A., Sampaio, J. L. M., . . . Gerberding, J. L. (2003). Extended-spectrum β-lactamase-producing *Klebsiella pneumoniae* in a neonatal intensive care unit: Risk factors for infection and colonization. *Journal of Hospital Infection, 53*, 198–206. doi:10.1053/jhin.2002.1373#

Pessoa-Silva, C. L., Toscano, C. M., Moreira, B. M., Santos, A. L., Frota, A. C. C., Solari, C. A., . . . Jarvis, W. R. (2002). Infection due to extended-spectrum β-lactamase-producing *Salmonella enterica* subsp. *enterica* serotype infantis in a neonatal unit. *Journal of Pediatrics, 141*(3), 381–387. doi:10.1067/mpd.2002.127279#

Petersen, L. R., Jamieson, D. J., Powers, A. M., & Honein, M. A. (2016). Zika virus. *New England Journal of Medicine, 374*, 1552–1563. doi:10.1056/NEJMra1602113#

Peterson, E. E., Meaney-Delman, D., Neblett-Fanfair, R., Havers, F., Oduyebo, T., Hills, S. L., . . . & Brooks, J. T. (2016). Update: Interim guidance for preconception counseling and prevention of sexual transmission of Zika virus for persons with possible Zika virus exposure–United States, September 2016. *Morbidity and Mortality Weekly Report, 65*(39), 1077–1081. doi:10.15585/mmwr.mm6539e1

Petribu, N. C. de L., Aragao, M. de F. V., van der Linden, V., Parizel, P., Jungmann, P., Araujo, L., . . . Duarte, M. D. C. M. B. (2017). Follow-up brain imaging of 37 children with congenital Zika syndrome: Case series study. *British Medical Journal, 359*, j4188. doi:10.1136/bmj.j4188#

Pierce, M., Kurinczuk, J.J., Spark, P., Brocklehurst, P., & Knight, M. (2011). Perinatal outcomes after maternal 2009/H1N1 infection: National cohort study. *British Medical Journal, 342,* d3214. doi:10.1136/bmj.d3214

Pierce, R., Lessler, J., Popoola, V. O., & Milstone, A. M. (2017). MRSA acquisition risk in an endemic NICU setting with an active surveillance culture and decolonization program. *Journal of Hospital Infection, 95*(1), 91–97. doi:10.1016/j.jhin.2016.10.022#

Popoola, V. O., Colantuoni, E., Suwantarat, N., Pierce, R., Carroll, K. C., Aucott, S. W., & Milstone, A. M. (2016). Active surveillance cultures and decolonization to reduce NICU *Staphylococcus aureus* infections. *Infection Control & Hospital Epidemiology, 37*(4), 381–387. doi:10.1017/ice.2015.316#

Puopolo, K. M. (2017). Bacterial and fungal infections. In E. C. Eichenwald, A. R. Hansen, C. R. Martin, & A. R. Stark (Eds.), *Cloherty and Stark's manual of neonatal care* (8th ed., pp. 684–719). Philadelphia, PA: Lippincott Williams & Wilkins.

Rabe, I. B., Staples, J. E., Villanueva, J., Hummel, K. B., Johnson, J. A., Rose, L., . . . Powers, A. M. (2016). Interim guidance for interpretation of Zika virus antibody test results. *Morbidity and Mortality Weekly Report, 65*(21). doi:10.15585/mmwr.mm6521e1

Raju, M., Salazar, J. C., Leopold, H., & Krause, P. J. (2007). Atovaquone and azithromycin treatment for babesiosis in an infant. *The Pediatric Infectious Disease Journal, 26*(2), 181–183. doi:10.1097/01.inf.0000250622.11505.8f

Ramos, E. R., Retzel, R., Jiang, Y., Hachem, R. Y., Chaftari, A. M., Chemaly, R. F., & Raad, I. I. (2011). Clinical effectiveness and risk of emerging resistance associated with prolonged use of antibiotic-impregnated catheters: More than 0.5 million catheter days and 7 years of clinical experience. *Critical Care Medicine, 39*(2), 245–251. doi:10.1097/CCM.0b013e3181feb83e

Rather, I. A., Kumar, S., Bajpai, V. K., Lim, J., & Park, Y.-H. (2017). Prevention and control strategies to counter Zika epidemic. *Frontiers in Microbiology, 8*, 305. doi:10.3389/fmicb.2017.00305#

Rather, I. A., Lone, J. B., Bajpai, V. K., Paek, W. K., & Lim, J. (2017). Zika virus: An emerging worldwide threat. *Frontiers in Microbiology, 8*, 1417. doi:10.3389/fmicb.2017.01417#

Rawal, G., Yadav, S., & Kumar, R. (2016). Zika virus: An overview. *Journal of Family Medicine and Primary Care, 5*(3), 523–527. doi:10.4103/2249-4863.197256#

Reagan-Steiner, S., Simeone, R., Simon, E., Bhatnagar, J., Oduyebo, T., Free, R., . . . U.S. Zika Virus Response Epidemiology and Surveillance Task Force Pathology Team. (2017). Evaluation of placental and fetal tissue specimens for Zika virus infection–50 states and District of Columbia, January-December, 2016. *Morbidity and Mortality Weekly Report, 66*(24), 636–643. doi:10.15585/mmwr.mm6624a3#

Regev-Yochay, G., Rubinstein, E., Barzilai, A., Carmelli, Y., Kuint, J., Etienne, J., . . . Keller, N. (2005). Methicillin-resistant *Staphylococcus aureus* in neonatal intensive care unit. *Emerging Infectious Diseases, 11*(3), 453–456. doi:10.3201/eid1103.040470

Reich, P. J., Boyle, M. G., Hogan, P. G., Johnson, A. J., Wallace, M. A., Elward, A. M., . . . Fritz, S. A. (2016). Emergence of community-associated methicillin-resistant *Staphylococcus aureus* strains in the neonatal intensive care unit: An infection prevention and patient safety challenge. *Clinical Microbiology and Infection, 22*(7), 645.e1–645.e8. doi:10.1016/j.cmi.2016.04.013#

Rice, L. B. (2006). Antimicrobial resistance in gram-positive bacteria. *American Journal of Infection Control, 34*, S11–S19. doi:10.1016/j.ajic.2006.05.220#

Rogalski, M. A., Gowler, C. D., Shaw, C. L., Hufbauer, R. A., & Duffy, M. A. (2016). Human drivers of ecological and evolutionary dynamics in emerging and disappearing infectious disease systems. *Philosophical Transactions of the Royal Society, B372*, 20160043. doi:10.1098/rstb.2016.0043

Saiman, L. (2006). Strategies for prevention of nosocomial sepsis in the neonatal intensive care unit. *Current Opinion in Pediatrics, 18*, 101–106. doi:10.1097/01.mop.0000193300.25141.c5

Saiman, L. (2016). Success of targeted strategies to reduce methicillin-susceptible *Staphylococcus aureus* infections in the neonatal intensive care unit. *Infection Control & Hospital Epidemiology, 37*(4), 388–389. doi:10.1017/ice.2016.24#

Saiz, J.-C., Martin-Acebes, M. A., Bueno-Mari, R., Salomón, O. D., Villamil-Jiménez, L. C., Heukelbach, J., . . . Pimentel-Coelho, P. M.

(2017). Zika virus: What have we learnt since the start of the recent epidemic? *Frontiers in Microbiology, 8*, 1554. doi:10.3389/fmicb.2017.01554#

Sakamoto, F., Yamada, H., Suzuki, C., Sugiura, H., & Tokuda, Y. (2010). Increased use of alcohol-based hand sanitizers and successful eradication of methicillin-resistant *Staphylococcus aureus* from a neonatal intensive care unit: A multivariate time series analysis. *American Journal of Infection Control, 38*(7), 529–534. doi:10.1016/j.ajic.2009.12.014

Sarda, V., Molloy, A., Kadkol, S., Janda, W. ., Hershow, R., & McGuinn, M. (2009). Active surveillance for methicillin-resistant *Staphylococcus aureus* in the neonatal intensive care unit. *Infection Control and Hospital Epidemiology, 30*(9), 854–860. doi:1086/605321

Satterfield-Nash, A., Kotsky, K., Allen, J., Bertolli, J., Moore, C. A., Pereira, I. O., . . . Peacock, G. (2017). Health and development at age 19-24 months of 19 children who were born with microcephaly and laboratory evidence of congenital Zika virus infection during the 2015 Zika virus outbreak–Brazil, 2017. *Morbidity and Mortality Weekly Report, 66*(49), 1347–1351. doi:10.15585/mmwr.mm6649a2

Scheans, P. (2010). Is your nursery full of MDROs? *Neonatal Network, 29*(6), 392–395. doi:10.1891/0730-0832.29.6.392

Seale, J., & Millar, M. (2014). Perinatal vertical transmission of antibiotic-resistant bacteria: A systematic review and proposed research strategy. *British Journal of Obstetrics and Gynecology, 121*, 923–928. doi:10.1111/1471-0528.12746#

Sengupta, A., Lehmann, C., Diener-West, M., Perl, T. M., & Milstone, A. M. (2010). Catheter duration and risk of CLA-BSI in neonates with PICCs. *Pediatrics, 125*(4), 648–653. doi:10.1542/peds.2009-2559#

Seybold, U., Halvosa, S. J., White, N., Voris, V., Ray, S. M., & Blumberg, H. M. (2008). Emergence of and risk factors for methicillin-resistant *Staphylococcus aureus* of community origin in intensive care nurseries. *Pediatrics, 122*(5), 1039–1046. doi:10.1542/peds.2007-3161#

Shah, A. J., Mulla, S. A., & Revdiwala, S. B. (2012). Neonatal sepsis: High antibiotic resistance of the bacterial pathogens in a neonatal intensive care unit of a tertiary care hospital. *Journal of Clinical Neonatology, 1*(2), 72–75. doi:10.4103/2249-4847.96753

Shah, P. S., & Kaufman, D. A. (2009). Antistaphylococcal immunoglobulins to prevent staphylococcal infection in very low birth weight infants. *The Cochrane Database of Systematic Reviews*, (2), CD006449. doi:10.1002/14651858.CD006449.pub2

Shakil, S., Ali, S. Z., Akram, M., Ali, S. M., & Khan, A. U. (2010). Risk factors for extended-spectrum β-lactamase producing *Escherichia coli* and *Klebsiella pneumoniae* acquisition in a neonatal intensive care unit. *Journal of Tropical Pediatrics, 56*(2), 90–96. doi:10.1093/tropej/fmp060#

Shan, C., Xie, X., Ren, P., Loeffelholz, M. J., Yang, Y., Furuya, A., . . . Shi, P.-Y. (2017). A rapid Zika diagnostic assay to measure neutralizing antibodies in patients. *EBioMedicine, 17*, 157–162. doi:10.1016/j.ebiom.2017.03.006#

Shapiro-Mendoza, C. K., Rice, M. E., Galang, R. R., Fulton, A. C., VanMaldeghem, K., Prado, M. V., . . . Zika Pregnancy and Infant Registries Working Group. (2017). Pregnancy outcomes after maternal Zika virus infection during pregnancy–U.S. Territories, January 1, 2016–April 25, 2017. *Morbidity and Mortality Weekly Report, 66*(23), 615–621. doi:10.15585/mmwr.mm6623e1#

Sharma, A., & Lal, S. K. (2017). Zika virus: Transmission, detection, control, and prevention. *Frontiers in Microbiology, 8*, 110. doi:10.3389/fmicb.2017.00110#

Sharma, D., Kumar, C., Pandita, A., Pratap, O. T., Dasi, T., & Murki, S. (2016). Bacteriological profile and clinical predictors of ESBL neonatal sepsis. *Journal of Maternal Fetal Neonatal Medicine, 29*(4), 567–570. doi:10.3109/14767058.2015.1011118#

Shea, K., & Jacobi, J. (2009). Maximizing the effectiveness of antibiotics: Challenges associated with multidrug gram-negative resistance and limited resources. *Contemporary Critical Care, 7*(4), 1–10.

Shirai, Y., Arai, H., Tamaki, K., Konishi, H., Kawase, Y., Shimizu, N., . . . Yoda, H. (2017). Neonatal methicillin-resistant *Staphylococcus aureus* colonization and infection. *Journal of Neonatal-Perinatal Medicine, 10*, 439–444. doi:10.3233/NPM-16166#

Shuford, J. A., & Patel, R. (2005). Antimicrobial growth promoter use in livestock–Implications for human health. *Reviews in Medical Microbiology, 16*(1), 17–24. doi:10.1097/00013542-200501000-00003

Silva, A. A. M., Ganz, J. S. S., Sousa, P. S., Doriqui, M. J. R., Ribeiro, M. R. C., Branco, M. R. F. C., . . . de Britto e Alves, M. T. S. S. (2016). Early growth and neurologic outcomes of infants with probable congenital Zika virus syndrome. *Emerging Infectious Diseases, 22*(11), 1953–1956. doi:10.3201/eid2211.160956

Silva, H. A., Pereira, E. M., Schuenck, R. P., Pinto, R. C. M., Abdallah, V. O. S., Santos, K. R. N., & Gontijo-Filho, P. P. (2009). Molecular surveillance of methicillin-susceptible *Staphylococcus aureus* at a neonatal intensive care unit in Brazil. *American Journal Infection Control, 37*, 574–579. doi:10.1016/j.ajic.2008.10.021#

Simões, P. M., Lemriss, H., Dumont, Y., Lemriss, S., Rasigade, J.-P., Assant-Trouillet, S., . . . Laurent, F. (2016). Single-molecule sequencing (PacBio) of the *Staphylococcus capitis* NRCS-A clone reveals the basis of multidrug resistance and adaptation to the neonatal intensive care unit environment. *Frontiers in Microbiology, 7*, 1991. doi:10.3389/fmicb.2016.01991#

Simon, A. K., Hollander, G. A., & McMichael, A. (2015). Evolution of the immune system in humans from infancy to old age. *Proceedings of the Royal Society B: Biological Sciences, 282*, 20143085. doi:10.1098/rspb.2014.3085#

Simonsen, K. A., Harwell, J. I., & Lainwala, S. (2011). Clinical presentation and treatment of transfusion-associated babesiosis in premature infants. *Pediatrics, 128*(4), e1019–e1024. doi:10.1542/peds.2010-0502

Singh, K., Gavin, P. J., Vescio, T., Thomson, R. B., Deddish, R. B., Fisher, A., . . . Peterson, L. R. (2003). Microbiologic surveillance using nasal cultures alone is sufficient for detection of methicillin-resistant *Staphylococcus aureus* isolates in neonates. *Journal of Clinical Microbiology, 41*(6), 2755–2757. doi:10.1128/JCM.41.6.2755-2757.2003#

Singh, N., Patel, K. M., Léger, M.-M., Short, B., Sprague, B. M., Kalu, N., & Campos, J. M. (2002). Risk of resistant infections with *Enterobacteriaceae* in hospitalized neonates. *The Pediatric Infectious Disease Journal, 21*(11), 1029–1033. doi:10.1097/00006454-200211000-00010

Singh, N., & Valsangkar, B. (2016). Health care-associated infections. In M. G. MacDonald & M. M. K. Seshia (Eds.), *Avery's neonatology: Pathophysiology & management of the newborn* (7th ed., pp. 982–993). Philadelphia, PA: Wolters Kluwer.

Snow, M. (2009). Babesiosis: Another tick-borne disease. *Nursing, 39*(6), 55. doi:10.1097/01.NURSE.0000352339.75395.f7#

Song, X., Cheung, S., Klontz, K., Short, B., Campos, J., & Singh, N. (2010). A stepwise approach to control an outbreak and ongoing transmission of methicillin-resistant *Staphylococcus aureus* in a neonatal intensive care unit. *American Journal of Infection Control, 38*(8), 607–611. doi:10.1016/j.ajic.2010.02.017#

Sotelo, J. R., Sotelo, A. B., Sotelo, F. J. B., Doi, A. M., Pinho, J. R. R., Oliveira, R. C., Bezerra, A. M. P. S., . . . Mangueira, C. L. P. (2017). Persistence of Zika virus in breast milk after infection in late stage of pregnancy. *Emerging Infectious Diseases, 23*(5), 854–856, doi:10.3201/eid2305.161538#

Soto, S. M. (2009). Relationship between virulence and antimicrobial resistance in bacteria. *Reviews in Medical Microbiology, 20*(4), 84–90. doi:10.1097/MRM.0b013e3283342903#

Souza, B. S. F., Sampaio, G. L. A., Pereira, C. S., Campos, G. S., Sardi, S. I., Freitas, L. A. R., . . . Soare, M. B. P. (2016). Zika virus infection induces mitosis abnormalities and apoptotic cell death of human neural progenitor cells. *Scientific Reports, 6*, 39775. doi:10.1038/srep39775#

Stapleton, P. J. M., Murphy, M., McCallion, N., Brennan, M., Cunney, R., & Drew, R. J. (2016). Outbreaks of extended spectrum beta-lactamase-producing Enterobacteriaceae in neonatal intensive care units: A systematic review. *Archives of Disease in Childhood Neonatal Edition, 101*(1), F72–F78. doi:10.1136/archdischild-2015-308707#

Stramer, S. L., Hollinger, F. B., Katz, L. M., Kleinman, S., Metzel, P. S., Gregory, K. R., & Dodd, R. Y. (2009). Emerging infectious disease agents and their potential threat to transfusion safety. *Transfusion, 49*(Suppl. 2), 1S–29S. doi:10.1111/j.1537-2995.2009.02279.x

Takei, Y., Yokoyama, K., Katano, H., Tsukiji, M., & Ezaki, T. (2010). Molecular epidemiological analysis of methicillin-resistant staphylococci in a neonatal intensive care unit. *Biocontrol Science, 15*(4), 129–138. doi:10.4265/bio.15.129

Tapsall, J. W. (2009). *Neisseria gonorrhoeae* and emerging resistance to extended spectrum cephalosporins. *Current Opinions in Infectious Diseases, 22*, 87–91. doi:10.1097/QCO.0b013e328320a836#

Tenover, F. C. (2006). Mechanisms of antimicrobial resistance in bacteria. *American Journal of Infection Control, 34*, S3–S10. doi:10.1016/j.ajic.2006.05.219#

Thorner, A. R. (2018). Epidemiology of pandemic H1N1 influenza ('swine influenza'). In E. L. Baron, (Ed.), *UpToDate*. Retrieved from https://www.uptodate.com/contents/epidemiology-of-pandemic-h1n1-influenza-swine-influenza

Toth, N. R., Chambers, R. M., & Davis, S. L. (2010). Implementation of a care bundle for antimicrobial stewardship. *American Journal of Health-System Pharmacists, 67*, 746–749. doi:10.2146/ajhp090259

Truven Health Analytics. (2018). Vancomycin. In *Micromedix pediatrics and Neofax standard* (electronic version). Ann Arbor, MI: Truven Health Analytics. Retrieved from http://neofax.micromedexsolutions.com/neofax

Tsai, M.-H., Chu, S.-M., Hsu, J.-F., Lien, R., Huang, H.-R., Chiang, M.-C., . . . Huang, Y.-C. (2014). Risk factors and outcomes for multidrug-resistant gram-negative bacteremia in the NICU. *Pediatrics, 133*(2), e322–e329. doi:10.1542/peds.2013-1248

Tsai, M.-H., Lee, I.-T., Chu, S.-M., Lien, R., Huang, H.-R., Chiang, M.-C., . . . Huang, Y.-C. (2016). Clinical and molecular characteristics of neonatal extended-spectrum β-lactimase-producing gram-negative bacteremia: A 12-year case-control-control study of a referral center in Taiwan. *PLoS One, 11*(8), e0159744. doi:10.1371/journal.pone.0159744

Tschoeke, D. A., Oliveira, L. S., Leomil, L., Tanuri, A., & Thompson, F. L. (2017). Pregnant women carrying microcephaly fetuses and Zika virus contain potentially pathogenic microbes and parasites in their amniotic fluid. *BMC Medical Genomics, 10*, 5. doi:10.1186/s12920-016-0242-1#

van der Eljk, A. A., van Genderen, P. J., Verdijk, R. M., Reusken, C. B., Mogling, R., van Kampen, J. J. A., . . . Koopmans, M. P. G. (2016). Miscarriage associated with Zika virus infection. *New England Journal of Medicine, 375*, 1002–1004. doi:10.1056/NEJMc1605898#

van der Linden, V., Filho, E. L. R., Lins, O. G., van der Linden, A., Aragão, M. F. V. V., Brainer-Lima, A. M., . . . Ramos, R. C. (2016). Congenital Zika syndrome with arthrogryposis: Retrospective case series study. *British Medical Journal, 354*, i3899. doi:10.1136/bmj.i3899#

van der Linden, V., Pessoa, A., Dobyns, W., Barkovich, J., van der Linden Júnior, H., Filho, E. L. R., . . . Moore, C. A. (2016). Description of 13 infants born during October 2015–January 2016 with congenital Zika virus infection without microcephaly at birth–Brazil. *Morbidity and Mortality Weekly Report, 65*(47), 1343–1348. doi:10.15585/mmwr.mm6547e2

Ventura, C. V., & Ventura, L. O. (2018). Ophthalmologic manifestations associated with Zika virus infection. *Pediatrics, 141*(Suppl. 2), S161–S166. doi:10.1542/peds.2017-2038E

Vrtis, M. C. (2008). Is your patient taking the right antimicrobial? *American Journing of Nursing, 108*(6), 49–55. doi:10.1097/01.NAJ.0000324377.09651.c7

Washam, M., Woltmann, J., Haberman, B., Haslam, D., & Staat, M. A. (2017). Risk factors for methicillin-resistant *Staphylococcus aureus* colonization in the neonatal intensive care unit: A systematic review and meta-analysis. *American Journal of Infection Control, 45*(12), 1388–1393. doi:10.1016/j.ajic.2017.06.021#

Wendelboe, A. M., Grafe, C., & Carabin, H. (2010). The benefits of transmission dynamics models in understanding emerging infectious diseases. *The American Journal of the Medical Sciences, 340*(3), 181–186. doi:10.1097/MAJ.0b013e3181e937ca

Women and Infants Pediatric Zika Algorithm. (2017). Retrieved from http://cnesites/sites/clinicianresources/wih/Shared%20Documents/Zika%20Algorithm.pdf

World Health Organization. (2013). *Emergency response framework*. Geneva, Switzerland: Author.

Yee-Guardino, S., Kumar, D., Abughali, N., Tuohy, M., Hall, G. S., & Kumar, M. L. (2008). Recognition and treatment of neonatal community-acquired MRSA pneumonia and bacteremia. *Pediatric Pulmonology, 43*, 203–205. doi:10.1002/ppul.20743#

Zervou, F. N., Zacharioudakis, I. M., Ziakas, P. D., & Mylonakis, E. (2014). MRSA colonization and risk of infection in the neonatal and pediatric ICU: A meta-analysis. *Pediatrics, 133*(4), e1015. doi:10.1542/peds.2013-3413

Zingg, W., Pfister, R., Posfay-Barbe, K. M., Huttner, B., Touveneau, S., & Pittet, D. (2011). Secular trends in antibiotic use among neonates: 2001–2008. *The Pediatric Infectious Disease Journal, 30*(5), 365–370. doi:10.1097/INF.0b013e31820243d3#

CHAPTER 27

Newborn or Infant Transplant Patient

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INTRODUCTION

Transplantation is not a common procedure in the neonatal period. The ability to perform various transplants has risen as technology has improved and knowledge of the physical processes has increased. Solid organ transplants such as liver, kidney, and heart are the most usual procedures. Use of stem cells is an exciting prospect for treating many limiting and sometimes fatal congenital diseases, but this therapy is surrounded by controversy regarding the ethics of its use. The ethics of transplantation in general is muddled when a child's life is at stake. However, it is not always in the infant's best interest to do these procedures.

Transplantation has become a reliable solution to infants suffering from end-stage organ disease. The ability to perform transplants has risen in the last decade due to policy changes, improved surgical techniques, improved donor allocation system, and development in the preservation of organs. Based on the National Data Report of the Organ Procurement and Transplantation Network (OPTN, 2019a), the number of transplanted organs in infants less than 1 year of age is 8,415. These are transplants performed in the United States from January 1, 1988 to April 30, 2019. In patients less than 1 year of age, the organs most often transplanted are the liver, heart, and intestine, with 4,758, 2,928, and 311 cases, respectively (OPTN, 2019a).

The success and outcome of the transplantation is a concerted effort from multiple disciplines and processes. It involves the early detection, accurate diagnosis and management of care, pretransplant evaluation and management, listing and finding the right donor, and intraoperative and posttransplant management. In this chapter, common types of transplants are discussed. Procurement of organs and cells is addressed. The procedure descriptions are meant to provide an overview. Key points to remember when working with infants and families undergoing transplants are the following:

- Infants are the most vulnerable transplant candidates. Great care and attention from multiple healthcare providers will determine the outcome of the transplant.
- Transplant nurses play an important role in solid organ transplantation.
- ABO blood type verification or ABO verification is for patient safety and it is strictly regulated.
- ABO incompatible transplants are proven to have good results in neonates or infant transplant recipients.
- Neonatal organ donation is becoming a viable solution to donor organ shortage.

LIVER TRANSPLANTATION IN INFANTS AND CHILDREN

Liver transplantation in recent years has become a viable solution to many destructive liver diseases. In infants and small children, especially those weighing less than 15 lb, a liver from a larger donor is "trimmed" to fit the small recipient. This has reduced the wait for an ideal matching donor. The technique is applied in living-related liver transplants when a segment of liver from a relative is removed and transplanted into the recipient. By using reduced-size and related donors, mortality has been reduced to as little as 4% in some transplant centers. Increase in survival has been coupled by reduced stay and a greater number of transplants being done for infants and children.

According to the OPTN and Scientific Registry of Transplant Recipients (SRTR) Annual Data Report 2010, the median number of months waiting for a liver-alone transplant for all blood types in pediatric recipients was 2.6 in 2009 (U.S. Department of Health & Human Services, 2017). The median waiting time for patients less than 1 year of age, listed from 2011 to 2014, is 119 days, whereas the median waiting time for patients 1 to 5 years of age, listed from 2011 to 2014, is 113 days (OPTN, 2018). Pretransplant mortality declined for patients wait-listed for a liver-alone transplant from 14.4 deaths per 100 wait-list years in 1998 to 8.2 in 2008. Patients on the waiting list aged younger than 6 years have the highest death rate, but this improved from 23.2 deaths per 100 wait-list years in 1998 to 14.9 in 2008. The number of deceased donor liver transplants has remained steady, while the number of living donor transplants decreased from a peak of 120 in 2000 to 51 in 2009. The rate of pediatric liver transplant has increased since 2002 to the current rate of 83.1 transplants per 100 patient-years on the waiting list. Patients aged 1 to 5 years are the most common recipients. Whites accounted for more than half of recipients. The most common etiology of liver disease was cholestatic disease. Among children and adolescents who underwent transplant in 2007 to 2009, 58% were on the waiting list for 60 days or less. Fifteen percent of patients were Status 1A at transplant, and 29% had a

model for end-stage liver disease (MELD)/pediatric end-stage liver disease (PELD) score of 30 or higher. Sixty-four percent of patients received a whole liver. Among living donor liver transplants, 72% were from related donors in 2009. Only a small number of transplants were from donation after cardiac death (DCD) donors.

According to the SRTR and OPTN 2016 Annual Report published in 2018 (Kim et al., 2018; OPTN & SRTR, 2018), patients less than 1 year of age remain the third most transplanted patients in the pediatric age group for liver transplantation. In 2016, there were over 700 new pediatric candidates added to the wait-list with the highest number in ages 1 to 5 years and 11 years and older (OPTN & SRTR, 2018). The median waiting time for patients less than 1 year of age, listed from 2011 to 2014, is 119 days, while the median waiting time for patients 1 to 5 years of age, listed during the same time period, is 113 days according to the OPTN Competing Risk Median Waiting Time to Decrease Donor Transplant for Registrations Listed: 2003 to 2014 based on OPTN data as of May 10, 2019 (OPTN, 2019a).

INDICATIONS FOR LIVER TRANSPLANTATION

According to Bucuvalas and Feng (2014), the data from the Studies of Pediatric Liver Transplantation (SPLIT) Registry shows that "biliary atresia is the most common underlying condition for liver transplantation, accounting for approximately 37% of the cases. Acute liver failure, retransplantation, and primary liver tumors including hepatoblastoma account for 13.5%, 10%, and 9% of transplants, respectively. Approximately 21.5% of the pediatric liver transplants are performed for inherited gene defects that can be categorized into (1) disorders of cholestasis (4.5%), (2) disorders of metabolism refractory to medical therapy, without cirrhosis (6%), and (3) disorders of metabolism that lead to structural liver injury (11%). The remaining cases comprise a heterogenous group of chronic conditions including cryptogenic cirrhosis, autoimmune hepatitis, sclerosing cholangitis, and mitochondrial hepatopathy. Disease recurrence is rare, occurring only in patients with autoimmune disease and in a subset of recipients with inherited disorders of cholestasis (Jara et al., 2009). As a result, liver disease distribution differs distinctly between children and adults as the latter is dominated by hepatitis C cirrhosis, alcoholic and nonalcoholic steatohepatitis, and hepatocellular carcinoma (Bucuvalas & Feng, 2014, p. 1390).

Etiology

"Acute liver failure is a severe hepatic dysfunction occurring within 8 weeks of onset of illness, with no known underlying chronic liver disease in patients from birth through 17 years of age with a liver-based coagulopathy (not corrected with vitamin K) with an INR ≥1.5 or PT ≥15 seconds in patients with encephalopathy or an INR ≥2.0 or PT ≥20 seconds in patients without encephalopathy" (Berquist et al., 2014, p. 5).

In neonates, acute liver failure (ALF) is a rare but often fatal event. Infants and younger children do not display the main symptom of ALF, hepatic encephalopathy, as do adults and older children. It is hard to diagnose and prove. Causes of ALF include congenital malformations, metabolic liver disease, hepatotoxins, idiopathic liver failure, malignant and benign neoplasms of the liver, infections, ischemic injury, congenital vascular or heart anomalies, and drugs.

Recognition of liver disease in a newborn is difficult because biochemical findings, such as hyperbilirubinemia and coagulopathy, may be due to various physiologic and pathophysiologic processes:

1. Hepatic encephalopathy is difficult to identify in any infant and almost impossible to distinguish from other metabolic encephalopathies in an ill neonate, especially if the infant requires ventilation support.
2. Because infants are so young, all neonatal liver failure tends to be labeled as "acute," which is consistent with the adult definition of a duration of less than 8 weeks. However, some infants clearly have liver failure from end-stage liver disease with cirrhosis due to liver damage that occurred during gestation (Jackson & Roberts, 2001). See Table 27.1 for examples.

Biliary Atresia

A progressive inflammatory process beginning shortly after birth is the hallmark of biliary atresia. Extrahepatic biliary atresia is the most common form. Biliary atresia occurs in 1 in 15,000 live births. The cause of the disease is unknown, but about 10% of the cases have other associated congenital defects of heart, blood vessels, intestine, and/or spleen involvement.

The Kasai procedure or Roux-en-Y hepatoportojejunostomy is the treatment for biliary atresia. Of newborns under 3 months of age undergoing this procedure, 80% will have reestablishment of their bile flow. The 20% remaining infants will not be helped by the procedure. A liver transplant is their only other treatment option (Esquivel, 2005).

Errors of Metabolism

Inherited errors of metabolism contribute greatly to liver failure and must be diagnosed promptly in the neonatal period. Galactosemia, hereditary fructose intolerance, and tyrosinemia are the most common metabolic diseases. Newborn screening by tandem mass spectrometry in many states tests for many metabolic diseases. These infants are being identified at a much earlier age than in previous years and treated when possible. An associated metabolic disease with acute liver disease is neonatal hemochromatosis

TABLE 27.1

CONDITIONS IN-UTERO POTENTIALLY LEADING TO LIVER DAMAGE

Tyrosinemia	*Fumarylacetoacetate hydrolase* deficiency	Autosomal recessive	OLT for fulminant neonatal form or OLT at about 2 years to avoid hepatocellular carcinoma
Urea cycle defects	*Ornithine transcarbamylase* deficiency *Carbamoyl phosphate synthetase* deficiency *Argininosuccinate synthetase* deficiency	X-linked dominant Autosomal recessive Autosomal recessive	OLT may be needed in the neonatal period to prevent irreversible CNS damage Variants may present in later childhood

CNS, central nervous system; OTP, orthotopic liver transplantation.

(NH). It is the most common cause of liver failure in infancy, linked with massive intrahepatic and extrahepatic iron disposition sparing the reticuloendothelial system (Dhawan & Mieli-Vergani, 2005). Despite chelation therapy, many severely affected infants will require transplantation.

"Biliary atresia is the number one indication of liver transplants in infants. However, primary transplantation without portoenterostomy is not recommended in patients with biliary atresia unless the diagnosis is made at an age greater than 120 days and a liver biopsy shows advanced cirrhosis" (Tiao, 2014, p. 1306).

"The pathogenesis of biliary atresia remains obscure despite numerous etiologic theories and investigations. It has been suggested that the disease is caused by (a) a failure of recanalization, (b) genetic factors, (c) defective morphogenesis, (d) ischemia/vascular lesions, (e) viruses, or (f) toxins. Currently, the most intriguing theory is that biliary atresia is the end result of 1 or more of these insults that then cause the biliary epithelium to become 'upregulated' to express the antigen on the cell surface" (Jones & Karrer, 2014, p. 710).

According to the Liver Kaplan-Meier Graft Survival Rates for Transplants Performed: 2008 to 2015 (OPTN, 2019a), recipients diagnosed with biliary atresia have a 737 functioning/alive graft 1-year post transplant, with a survival rate of 91.3% and a 89.2%, 93.1%, 95% confidence interval.

The indications for liver transplantation for children with metabolic liver disease according to the OPTN are alpha-1 antitrypsin deficiency A-1-A, Wilson's disease, hemochromatosis-hemosiderosis; metabolic disease: other specify, tyrosinemia, primary oxalosis/oxaluria-hyper, glycogen storage disease type IV (GSD-IV), glycogen storage disease type I (GSD-I), hyperlipidemia-II-homozygous Hy (OPTN, n.d.).

"The decision to perform liver transplant in patients diagnosed with metabolic disease causing structural liver damage is based on the PELD score, medical urgency and the survival benefit. In patients without structural damage, the aim is to prevent damage to extra hepatic organ(s) occurring consequent to the gene defect" (Bucuvalas & Feng, 2014, p. 1391).

CONTRAINDICATIONS FOR LIVER TRANSPLANTATION

There are many contraindications or reasons why transplantation should not be performed: (1) positive test for AIDS or HIV, (2) cancer outside the liver, (3) infection outside the liver, (4) technical infeasibility, and (5) other medical problems such as heart disease, lung failure, or epilepsy that would interfere with the success of the transplant (Esquivel, 2005).

"The contraindications to transplant include: (1) Primary unresectable extrahepatic malignancy, (2) progressive terminal nonhepatic disease, (3) uncontrolled systemic sepsis, and (4) irreversible neurologic injury. Relative contraindications to transplantation that must be individually evaluated include: (1) serology positive for HIV, (2) advanced or partially treated systemic infections, and (3) severe psychosocial abnormalities" (Tiao, 2014, p. 1308).

TRANSPLANT SELECTION

The advent of partial liver transplant and the use of living liver donors has eased transplant selection. Not all patients can receive a transplant. A liver function test based on the hepatic conversion of lidocaine to monoethylglycinexylidide (MEGX) can give prognostic information. This test has been used because of its rapid turnaround for real-time assessment of hepatic function in transplantation. The MEGX test is a useful tool that can improve the decision-making process with respect to the selection of transplant candidates. Patients with a MEGX 15- or 30-minute test value less than 10 mcg/L have a particularly poor 1-year survival rate. Serial monitoring of liver graft recipients early after transplantation with the MEGX test may initially alert the clinician to a major change in liver function; if used with other tests, such as serum hyaluronic acid concentrations, it may become more discriminatory. In critically ill patients, several studies have shown that an initially rapid decrease in MEGX test values is associated with an enhanced risk for the development of multiple organ dysfunction syndromes and a poor outcome. Further, this decrease appears to be associated with an enhanced systemic inflammatory response (Oellerich & Armstrong, 2001).

"Each liver transplant candidate is assigned a score that reflects the probability of death within a 3-month period as determined by the Model for End-Stage Liver Disease (MELD) scoring system or the Pediatric End Stage Liver Disease (PELD) scoring system. Liver candidates can also be assigned a priority status if the candidate meets the requirements for that status" (OPTN, 2019, p. 147).

"Liver candidates less than 18 years old at the time of registration may be assigned *any* of the following:

- Pediatric status 1A
- Pediatric status 1B
- Calculated MELD or PELD score
- Exception MELD or PELD score
- Inactive status" (OPTN, 2019, p. 147).

A pediatric Status 1A is assigned if the candidate meets the criteria defined by OPTN Policy 9.1.A. A candidate must be less than 18 years old and have one of the following conditions: (1) Fulminant liver failure without pre-existing liver disease, defined as the onset of hepatic encephalopathy within 56 days of the first signs and symptoms of liver disease, (2) Primary non-function of a transplanted liver within 7 days of transplant, (3) Hepatic artery thrombosis (HAT), and (4) Acute decompensated Wilson's disease" (see OPTN Policies for complete data; OPTN, 2019b).

Patients who do not meet the criteria for pediatric Status 1A or whose MELD/PELD score does not coincide with the severe condition presented but meets the criteria specified by OPTN Policy 9.3.C are eligible for MELD or PELD score exceptions. The Specific Standardized MELD/PELD exceptions are (1) cholangiocarcinoma, (2) cystic fibrosis, (3) familial amyloid polyneuropathy (FAP), (4) hepatic artery thrombosis (HAT), (5) hepatocellular carcinoma (HCC), (6) hepatopulmonary syndrome (HPS), (7) metabolic disease, (8) portopulmonary hypertension, and (9) primary hyperoxaluria (OPTN, 2019b, Table 9.2; see Policy 9.3.C for complete data.)

For purposes of Status 1A/1B definition and classification, candidates listed at less than 18 years of age who remain on or have returned to the waiting list on or after reaching age 18 may be considered Status 1A/1B and shall qualify for other pediatric classifications under the following criteria. There are five allowable diagnostic groups: (i) fulminant liver failure; (ii) primary nonfunction; (iii) hepatic artery thrombosis; (iv) acute decompensated Wilson's disease; and (v) chronic liver disease. Candidates meeting criteria (i), (ii), (iii), or (iv) may be listed as a Status 1A; those meeting criteria (v) may be listed as a Status 1B.

ESTIMATION SCALES OF LIVER ALLOCATION

The MELD and PELD are numerical scales that are currently used for liver allocation. The MELD and PELD scores are based on a patient's risk of dying while waiting for a liver transplant and are

based on objective and verifiable medical data. United Network for Organ Sharing (UNOS, 2005) uses the PELD for patients who are under 12 years old. The PELD score is calculated using the following:

Albumin (g/dL)
Bilirubin (mg/dL)
International normalized ratio (INR)
Growth failure (based on gender, height and weight ratio)
Age at listing

PRETRANSPLANT MANAGEMENT

The care of infants and children before transplantation is significant in the outcome of the transplant. "In order for a pediatric candidate to be medically and psychosocially optimized at the time of transplantation, the transplant team must develop processes to (1) address patient and family education; (2) maximize access to suitable organ, living or deceased; (3) optimize nutritional status; (4) prevent infection; and (5) prevent and/or treat complications of portal hypertension" (Bucuvalas & Feng, 2014, p. 1392).

Quality and Safety: Management of infants and children before the transplant is paramount for success. So-called spiffing up to improve the clinical status of the patient before surgery could include normalizing electrolyte imbalances, improving nutrition, decreasing ascites and edema, improving diuresis, and giving blood transfusions if indicated. Infants and children who have severe renal insufficiency are placed on continuous venovenous hemofiltration (CVVH) or continuous venovenous hemodialysis (CVVHD) and brought to the operating room with the CVVH machine.

Nutritional Support

The nutritional status of infants and children prior to and after transplantation is significant in the success of the transplant. According to Bucuvalas and Feng (2014), children who are able to achieve an optimal nutritional status have lesser complications post transplant (Bucuvalas & Feng, 2014, p. 1392). Nutrition is best achieved enterally. Effective enteral administration is not always possible with patients with liver failure because of impaired absorption. Total parenteral nutrition (TPN) may be needed to support hepatocellular function and improve altered metabolism and absorption. A thorough assessment of nutritional status can be difficult because of metabolic disturbances. The balanced dietary approach moderated to replenishment of substrates and calories as needed helps prevent complications. Protein is needed to maintain lean body mass and preserve organ function (Pomposelli & Burns, 2002).

Based on the data from the SPLIT Registry, 40% of transplant candidates less than 2 years old are more than 2 standard deviations below norms for growth at time of transplant (Buculavas & Feng, 2014, p. 1392).

PRETRANSPLANT EVALUATION

During the pretransplant evaluation, the recipient's immunizations should be updated. Since the recipient's response to vaccinations may be suboptimal, it is recommended that vaccination should be given as soon as possible (Kline, 2014).

Recommended vaccinations:

1. Inactivated polio virus
2. Tetanus-diphtheria toxoid
3. Influenza (yearly)
4. Pneumococcal
5. Varicella (if nonimmune)
6. Hepatitis B
7. Hepatitis A (if nonimmune)
8. Haemophilus influenzae type b (pediatric candidates)
9. Measles–mumps–rubella (pediatric candidates)
10. Meningococcal vaccine (particularly for patients entering college within the next 1–2 years; Hockenberry-Eaton, 1998, p. 137)

"Pediatric candidates . . . must wait at least 4 weeks between administration of live vaccines and transplant procedure for *all* adult and pediatric candidates" (Dumas-Hicks, Fitzmorris, Cassidy, & Canales, 2017, p. 132).

PREPARING THE PATIENT FOR THE OPERATING ROOM (OR)

Infants and small children transplant candidates are either already admitted in the intensive care unit or in surgical–medical units for evaluation and workup. Transplant centers or hospitals have their own pretransplant protocols. The checklist may include but is not limited to the following:

a. Laboratory panels
b. Transfusion orders
c. Diagnostic imaging
d. Biopsy
e. Preoperative orders such as nothing by mouth, preoperative bath, and chlorhexidine gluconate (CHG) wipes, as well as induction of immunosuppressive agents
f. Consent and updated history and physical

Most transplant recipients are admitted in the ICU, but in some cases patients are at home waiting or in a nearby housing facility. For patients who are already admitted, the hospital pretransplant protocol or checklist is initiated. The checklist would include but is not limited to the following:

a. Laboratory panels
b. Transfusion orders
c. Immunosuppressant drugs and antibiotics are ordered to go to OR
d. Patient is kept NPO
e. Verification of consent and updated history and physical
f. Preoperative bath given and CHG wipe prior to transport to the OR

For outpatients, the transplant coordinator contacts the family when a donor organ becomes available. The patient is then brought to the hospital, and on admission, the inpatient pretransplant checklist is initiated.

Nursing Care in the Operating Room

The circulating transplant nurse has a unique role in the OR. The nurse provides education to families and transplant patients in the preoperative setting and provides direct care to the patient intraoperatively.

Responsibilities of the Circulating Transplant Nurse:

- Provide safe and effective environment
- Assist anesthesia team
- Ensure compliance with UNOS and OPTN regulations, that is, ABO verification
- Track organ ischemia time
- Appropriate tissue and extra vessel handling and storage

Infants and small children require specific care in the OR. One of the many roles of the nurse is to keep the patient thermodynamically stable by maintaining optimum room temperature. Because

the surgery involves a rather wide abdominal incision, the patient will be exposed to extreme temperatures for the entirety of the procedure. A typical liver transplant surgery can last for 10 to 12 hours. Thus, it is imperative that the nurse provides measures to prevent heat loss. One of the many ways to keep infants warm in the OR is to wrap the infant's limbs or extremities in cotton padding and plastic drape. Place a warming device and absorbent padding under the patient and use a radiant heat lamp if possible. Monitor the patient's temperature and provide warm irrigating solutions in the sterile field.

The nurse also helps the anesthesia team by checking blood products and making sure that they are available at all times. Time is crucial in the delivery of blood products to infants and small children in the OR.

Another important role of the nurse is initiating the ABO verification of the intended recipient and donor. The ABO verification of donor organs and intended recipients during the pretransplant and transplant phase has received meticulous and rigorous attention from UNOS, Organ Procurement and Transplantation Network Board, and Center for Medicare and Medicaid Services (CMS) in the last several years. Because organ transplantation is a highly regulated program, the implementation and compliance of ABO verification has a major impact on the existence of said program.

The UNOS/OPTN Board had implemented the following modification to the policies and requirements for ABO verification on June 23, 2016:

- Policy 5.7 Organ Check-in states that the transplant hospital must complete an organ check-in any time an organ is recovered outside the facility where the transplant will take place. The organ check-in must be completed upon arrival at the transplant hospital prior to opening the organ's external transport container.
- Policy 5.8 Pretransplant Verification is the verification of the donor and recipient using source documents as required by OPTN.
- Policy 5.8.A Pretransplant Verification Prior to Organ Receipt states that if the recipient's surgery will begin prior to organ receipt in the OR, the transplant hospital must conduct a pretransplant verification that meets all the current OPTN requirements.
- Policy 5.8.B Pretransplant Verification Upon Organ Receipt states that the transplant hospital must conduct a second verification at the time of organ receipt in the OR, prior to anastomosis and must meet all the current OPTN requirements (OPTN, 2016).

TYPES OF LIVER TRANSPLANTS

"The transplant procedure is carried out through a bilateral subcostal with midline extension incision. Meticulous ligation of portosystemic collaterals and vascularized adhesions is necessary to avoid slow but relentless hemorrhage. Dissection of the hepatic hilum, with provision for division of the hepatic artery and portal vein above their bifurcation, allows maximal recipient vessel length. The bile duct, when present, is divided high in the hilum to preserve the length and vasculature of the distal duct in case it is needed for later reconstruction. Preservation of the Roux-en-Y in biliary atresia patients who have undergone portoenterostomy simplifies biliary reconstruction. . . . In children with serious vascular instability who cannot tolerate caval occlusion or in patients undergoing transplantation using a left lateral segment, 'piggy-back' implantation is required. In this procedure, the recipient vena cava is left intact, and partial caval occlusion allows end-to-side implantation of a donor hepatic vein patch" (Tiao, 2014, p. 1310).

The orthotopic approach requires replacing the recipient liver with the donor liver. After the donor liver is removed, preserved, and packed for transport, it must be transplanted into the recipient within 12 to 18 hours. The surgery begins by removing the diseased liver from the four main blood vessels and other structures that hold it in place in the abdomen. After the recipient's liver is removed, the new healthy donor liver is then connected and blood flow is restored. The final connection is made to the bile duct, a small tube that carries bile made in the liver to the intestines.

Heterotopic Liver Transplantation

In heterotopic liver transplantation, the recipient's liver is left in place and a donor liver is sewn into an ectopic site (UNOS, 2005). The advantage to this transplant is that the patient retains the original liver with the donor liver helping. It is not as common as other types of liver transplantation in recent years.

Reduced-Size Liver Transplantation

In reduced-size liver transplantation, allografts of donor liver are divided into eight pieces, each supplied by a different set of blood vessels. Two of these pieces have been enough to save a patient in liver failure, especially if the patient is a child. It is therefore possible to transplant one liver into at least two patients. Liver tissue grows to accommodate its job so long as there is initially enough of the organ to use. Patients have survived with only 15% to 20% of their original liver, provided the 15% to 20% was healthy (Boudi, 2019).

"When left lateral segment reduced-size grafts are used, the left hepatic vein orifice is anastomosed directly to the anterolateral surface of the infradiaphragmatic IVC (inferior vena cava). The left lateral segment allograft is later fixed when necessary to the undersurface of the diaphragm to prevent torsion and venous obstruction of this anastomosis. Fixation is unnecessary with right/left lobe grafts or with a whole organ" (Tiao, 2014, p. 1310).

Living Donor Transplantation

Living donor liver transplantation (LDLT) is a procedure in which a healthy, living person donates a portion of his or her liver to another person. The feasibility of LDLT was first demonstrated in the United States in 1989. The recipient was a child, who received a segment of his mother's liver. In the pediatric experience, survival of the recipient child and function of the transplanted liver (graft) at 1 year is about 90%. The transplanted liver grows to almost full size within 6 to 8 weeks and begins to function fully.

Based on the OPTN National Data, the number of living donor liver transplants performed in pediatric transplant recipients aged less than 1 yr is 4770 and 6518 for ages 1 to 5 years old., from January 1,1988 to May 31,2019 (OPTN, 2019a; see OPTN National Data for complete data). "In most pediatric cases, the left lateral segment donated from an adult is used as a graft. In situ dissection of the left lateral segment, preserving the donor vascular integrity until the parenchymal division is completed, is undertaken" (Tiao, 2014, p. 1310).

Auxiliary Liver Transplantation

There are three levels of cells in the hepatic lineage that respond to injury: the mature hepatocyte, the ductular "bipolar" progenitor cell, and a putative periductular stem cell. Hepatocytes are numerous and respond rapidly to liver cell loss by one or two cell cycles.

The ductular progenitor cells are less numerous, may proliferate for more cycles than hepatocytes, and are generally considered "bipolar," that is, they can give rise to biliary cells or hepatocytes. Periductular stem cells, although rare in the liver, can proliferate for a long time. Extrahepatic (bone marrow) origin of the periductular stem cells is supported by recent data showing that hepatocytes may express genetic markers of donor hematopoietic cells after bone marrow transplantation.

These different regenerative cells with variations in potential for proliferation and differentiation may provide different sources of cells for liver transplantation: hepatocytes for treatment of acute liver damage, liver progenitor cell lines for liver-directed gene therapy, and bone marrow-derived cells for chronic long-term liver replacement. A limiting factor in the success of liver cell transplantation is the condition of the hepatic microenvironment in which the cells must proliferate and set up housekeeping.

Few liver stem cell transplantations have taken place. Cases of mold and other infections have been associated with liver stem cell transplantations. Further evaluation is warranted before such transplantation is accepted as a therapy in end-stage liver disease.

PORTAL HYPERTENSION

Portal hypertension is abnormally high blood pressure in the portal vein, the primary vein that brings blood from the intestine to the liver. When this vein clots or when the liver develops scar tissue from disease and compresses the vein, the blood pressure in the vein goes up and portal hypertension develops. **Emergency Alert: In most patients, portal hypertension develops regardless of primary disease process with progressive cirrhosis.**

The liver normally filters blood from the abdominal organs. Portal hypertension can prohibit the liver from doing its job by causing the growth of collaterals that connect blood flow from the intestine to the general circulation, bypassing the liver. When this occurs, substances that are normally removed by the liver pass into general circulation. If not treated, portal hypertension can be progressive and cause serious complications. Pharmacologic management with medications such as vasopressin and octreotide has been used for acute portal hypertension. Complications of portal hypertension can include esophageal varices complicated by hemorrhage and hypersplenism. Treatment with endoscopic sclerotherapy has emerged as an effective treatment for bleeding esophageal varices. Sclerotherapy is the ideal, safe, and effective treatment for bleeding esophageal varices; it prevented bleeding in 88.1% of patients after variceal eradication (Zargar et al., 2004). Though rarely used, the Sengstaken–Blakemore tube can achieve direct balloon tamponade of bleeding varices or transthoracic ligation of the bleeding.

Splenectomy is used for older children when hypersplenism and splenic sequestration of blood components is noted (leukopenia, thrombocytopenia, or anemia). In neonates and small children, splenectomy is rarely done as fatal sepsis is a major complication; functional disorders, such as ascites and thrombocytopenia, should be treated with a more conservative approach.

INFECTION

Infants and children are compromised, as their immune system is still developing. End-stage liver disease further decreases their ability to fight off any infections. They are especially vulnerable to infections normally seen during childhood such as colds, flu, and other childhood diseases (e.g., meningitis, otitis media, and pneumonia). Nosocomial exposure in the hospital from invasive procedures (liver biopsy, intravenous [IV] lines) and handling by the healthcare team further jeopardize the patient for infections. Standard precautions must be followed. According to the indications from the Centers for Disease Control and Prevention (CDC), infection can be decreased by as much as half with attention to handwashing, draping for procedures, rubbing IV hubs with alcohol at least 30 seconds before using them, use of disinfectant before invasive events, and discontinuance of lines on a timely basis. Antibiotics are used when indicated by culture and sensitivity.

Vaccinations should be given to infants and children on a routine, scheduled basis when possible. Other immunizations advised before transplantation include hepatitis B, hepatitis A, and influenza for older children. Respiratory syncytial virus (RSV) is the most common cause of bronchiolitis and pneumonia among infants and children under 1 year of age. RSV is highly infectious and almost all babies get it before the age of 2. Palivizumab (Synagis; MedImmune, Gaithersburg, MD) is given for neonates at risk for RSV before transplant on a monthly basis.

POSTTRANSPLANT MANAGEMENT

Posttransplant management would include care given to any postoperative patient. Blood gases, laboratory reports, fluid balance, urinary output (1–2 mL/kg), and IV access are as usual watched closely. Drainage from the liver transplant is closely observed. Dark, black, bloody discharge can mean that the circulation to the transplant is not working and the liver may be dead.

Prophylactic antibiotics are given before, during, and after surgery. Antifungal and anti–herpes virus prophylaxis is also given.

Immunosuppressive Management

Immunosuppressive management usually starts with prednisone in infants and children. The calcineurin inhibitors, cyclosporine and tacrolimus, are also used; they have distinct advantages and drawbacks. It is important to tailor their use to the patient's tolerance. In some patients, the need to ameliorate the adverse effects of tacrolimus may necessitate a switch to cyclosporine-based therapy and vice versa. Some centers use azathioprine as part of an initial cyclosporine immunotherapy program. It is usually discontinued early in the posttransplant period.

Rejection is treated with steroid pulses, steroid recycling, or the monoclonal anti–T cell antibody muromonab-CD3 (Orthoclone OKT3). **Quality and Safety: Daily monitoring of immunosuppressive medications is necessary for proper dose adjustment in infants and children.** Rescue therapy with a cyclosporine microemulsion (Neoral, Novartis Pharmaceuticals Corporation, East Hanover, NJ)–based regimen for transplant patients intolerant of tacrolimus has been evaluated to assess the best method of switching and determining the initial and maintenance doses in children. Transplant centers are evaluating this therapy at present.

Drugs used for immunosuppression have been implicated in causing numerous long-term side effects including nephrotoxicity, glucose intolerance, and hyperlipidemia. Calcineurin inhibitors are known to cause nephrotoxicity, which is of concern in pediatric liver transplant recipients. Almost all patients will require antihypertensive therapy. Posttransplant malignancies are among the most important complications in organ transplantation.

"Rather than using induction to augment overall immunosuppression and reduce rates of acute rejection, induction immunosuppression is now used to facilitate minimization or even complete avoidance of corticosteroids and/or reduction of exposure to calcineurin inhibitors while maintaining stable rates of acute rejection, graft, and patient survival. Currently, induction is administered to

31% of pediatric liver transplant recipients. The dominant choice for induction has been anti-interleukin-2 (IL-2) receptor antibodies, over antithymocyte globulin (Di Filippo, 2005). Historically, two IL-2 receptor antibodies have been available, basiliximab and daclizumab, but the latter is no longer available. In general, the IL-2 receptor antibodies have had an excellent safety profile with no increase in hemodynamic, metabolic, nephrologic, neurologic, infectious or malignant adverse events including post-transplant lymphoproliferative disease" (Bucuvalas & Feng, 2014, p. 1395).

POSTOPERATIVE COMPLICATIONS

Most complications after liver transplantation are heralded by an increase in hepatocellular enzymes, often associated with malaise, fever, leukocytosis, and jaundice. The clinical picture defines hepatic allograft dysfunction, but it does not separate allograft rejection from other allograft complications such as primary nonfunction, bile duct abnormalities, hepatic artery thrombosis, or allograft infection. The use of real-time and Doppler ultrasonography to assess hepatic vasculature and the use of CT and MRI are often necessary. Allograft biopsy is definite when the cause of the graft abnormality is rejection; it can strongly support the diagnosis of viral infection or cholangitis when the characteristic histologic markers and microscopic appearance are seen. Definitive diagnosis of the cause of the allograft dysfunction should precede immunologic manipulation (OPTN, 2012).

POSTTRANSPLANT MANAGEMENT OF COMPLICATIONS

Most patients are taken to the pediatric intensive care unit (PICU), intubated, and monitored for the following:

1. Hypothermia—common in infants due to prolonged exposure of the abdominal viscera during surgery; careful monitoring of patient's body temperature is needed to prevent dysrhythmias, clotting abnormalities, impaired renal function, and delayed wound healing.
2. Hemorrhage—increased blood in Jackson-Pratt drains, increased abdominal girth, oozing from suture line, and change in cardiovascular status will require blood products such as fresh frozen plasma (FFP), platelets, and cryoprecipitate.
3. Fluid and electrolyte imbalance—decreased urine output less than 1 mL/kg/hour may indicate early graft dysfunction or nephrotoxicity; electrolytes monitoring is required every 6 hours.
4. Neurologic status—encephalopathy/ hepatic coma may indicate bad liver; "getting the shakes"—may indicate elevated levels of Prograf.
5. Gastrointestinal status—watch for abdominal distention, rigid or painful abdomen; stool color and consistency.
6. HAT—most common postoperative complication; watch for sudden spike in temperature, abdominal pain with increased liver function tests (LFTs), change in mental status, and biliary leaks.
7. Portal vein thrombosis—presents with variceal bleeding or a slowly enlarging liver or spleen and low platelet count.
8. Biliary leaks—leading cause of morbidity and mortality in children; a change in the color of fluid in the Jackson-Pratt drains noted in the immediate postoperative period; will need surgical intervention.
9. Rejection—early signs include low-grade fever, increased liver enzymes and bilirubin, pain over graft, irritability, and ascites.

"In infants and small children, the challenge is to anastomose very small recipient blood vessels to donor graft. Because of the anatomical features of recipient and donor, the risk for surgical complications in infants and small children is relatively high. The common immediate post-op transplant complications are vascular and biliary complications. The vascular complications involves the main vessels of anastomoses, specifically hepatic artery thrombosis, portal vein stenosis or obstruction and venous outflow obstruction (Bucuvalas & Feng, 2014, p. 1394).

HEART TRANSPLANT

"The first pediatric heart transplant was performed by Kantrowitz and colleagues at the Maimonides Medical Center in Brooklyn, New York on December 6, 1967. Three days prior to the first transplant, Christiaan Barnard performed the first cardiac allotransplantation in South Africa.

Donor organs for infants and small children are still very limited thus increasing time on waiting list. Because of this shortage, the use of ABO incompatible transplants has recently been advocated by the Toronto group for neonatal and infant candidates, since antibodies to the major blood group antigens are not produced until later in infancy" (Webber, 2014, p. 1407). West (2011) concluded in her report that "ABOi (ABO incompatible) heart transplantation has shown to be safe early in childhood and allows improved access to donor organs. ABO-related AMR has been reported only rarely; long-term outcomes are comparable with ABOc (ABO compatible) transplantation. Limits of suitability based on age or other indicators of maturity are still undetermined" (p. 553).

The OPTN Network Heart Allocation Classifications and Ranking Policy includes Eligibility for Intended Blood Group Incompatible Offers for Deceased Donor Hearts (OPTN, 2019b, Policy 6.6.B).

"The candidate will be eligible for intended blood group incompatible heart offers if the candidate meets at least *one* of the following conditions:

1. Candidate is less than one year old at the time of the match run, and meets *both* of the following:
    1. Is registered as status 1A or 1B.
    2. Has reported isohemagglutinin titer information for A or B blood type antigens to the OPTN contractor within the last 30 days.
2. Candidate is at least one year old at the time of the match run, and meets all of the following:
    1. Is registered prior to turning two years old.
    2. Is registered as status 1A or 1B.
    3. Has reported to the OPTN Contractor isohemagglutinin titers less than or equal to 1:16 for A or B blood type antigens from a blood sample collected within the last 30 days. The candidate must not have received treatments that may have reduced isohemagglutinin titers to 1:16 or less within 30 days of when this blood sample was collected" (OPTN, 2019b, p. 110).

Based on the 2016 OPTN/SRTR Annual Data Report (Colvin et al., 2018), 624 new pediatric candidates were added to the heart transplant waiting list, with few at inactive status. At year-end 2016, 367 candidates listed before their 18th birthdays were awaiting heart transplant, 69.8% active. Over the past decade, the number of candidates listed as inactive status decreased from 178 in 2006 to 111 in 2016. The largest pediatric age group on the waiting list in 2016 was 11 to 17 years (34.2%), followed by ages younger than 1 year (27.7%), 1 to 5 years (23.4%), and 6 to 10 years (14.7%). According to the OPTN National Data, there

were 2,928 heart transplants performed in the United States on patients less than 1 year of age from January 1, 1988 to April 30, 2019 (OPTN, 2019a).

With the advent of new surgical techniques, younger and smaller patients are having heart transplants. The availability of organs is limited for small children. Many centers try to wait until the child is larger to accommodate a larger heart. Developmental studies have shown that young infants and children are at risk for growth failure, developmental delays, and serious neurologic sequelae.

INDICATIONS FOR HEART TRANSPLANT

Heart transplantation in infants and small children is usually the only way or the last resort to save a patient's life. The primary indications for heart transplant are dilated cardiomyopathy and complex congenital heart defects. Diagnoses leading to transplantation are age dependent, with congenital heart defects accounting for over half of transplants in the infant age group, and cardiomyopathy accounting for almost two-thirds among adolescents (Webber, 2014, p. 1407).

The Common Causes of Heart Failure

The common causes of heart failure in the newborn period are

a. Fetal–maternal transfusion
b. Myocarditis
c. Cardiomyopathy
d. Anemia of Rh sensitization
e. Fetal and postnatal arrhythmias
    i. Congenital complete heart block
    ii. Supraventricular arrhythmia
f. Birth asphyxia
g. Sepsis
h. Hypoglycemia
i. Hypocalcemia
j. Severe anemia
k. Congenital structural heart defects

The common causes of heart failure during infancy are

a. Structural defects
b. Cardiomyopathy
c. Myocarditis
d. Arrhythmias
e. Renal failure
f. Systemic hypertension
g. Hypothyroidism
h. Adrenal insufficiency

(Seattle Children's Hospital, 2015).

Bridge to Transplant

Heart failure due to congenital defects and organ deterioration affects the entire body. Many patients waiting for a heart transplant are so debilitated that they may not be able to tolerate the surgery. To assist the body and improve the patients' physical status, several modalities are used to help the patient gain strength while awaiting transplant—hence a "bridge to transplant." Devices commonly used for bridge to transplant are the left ventricular–assist device (LVAD), extracorporeal membrane oxygenation (ECMO), and, on a limited basis, the Berlin Heart.

Left Ventricular–Assist Device

The LVAD is an implantable mechanical device to pump blood through the body. It takes over the work of the failing heart. Bridge-to-transplant facilities that have an aggressive approach to implantable LVAD placement may substantially improve the survival rate of patients with postcardiotomy heart failure (Garbade, Bittner, Barten, & Mohr, 2011).

Extracorporeal Membrane Oxygenation

ECMO currently comes in two varieties: venoarterial (VA) and venovenous (VV). VA ECMO takes deoxygenated blood from a central vein or the right atrium, pumps it past the oxygenator, and then returns the oxygenated blood, under pressure, to the arterial side of the circulation (typically, to the aorta). This form of ECMO partially supports the cardiac output as the flow through the ECMO circuit is in addition to the normal cardiac output.

VV ECMO takes blood from a large vein and returns oxygenated blood back to a large vein. VV ECMO does not support the circulation. VA ECMO helps support the cardiac output and delivers higher levels of oxygenation support than does VV ECMO. VA ECMO carries a higher risk of systemic emboli than does VV ECMO. The normalization of left heart filling pressures alleviates pulmonary edema and improves the child's physical status.

Berlin Heart

The Berlin Heart (Berlin Company, Berlin, Germany) has been used for infants and small children who can utilize neither LVAD nor ECMO. Named after the company in Berlin, Germany, that manufactures it, the Berlin Heart is a ventricular-assist device that works by helping the right ventricle of the heart pump blood to the lungs and the left ventricle to pump blood to the rest of the body. The bulk of the Berlin Heart is located outside of the body, with only the pumps connected to the heart emerging from the body. The device is run by a laptop. The Berlin Heart comes in various sizes for a range of patients and is the only mechanical heart small enough to be used in very young children.

Great consideration is taken when determining the right-size donor for an infant or small child recipient. For orthotopic heart transplant, the most common technique is the bicaval anastomosis. "The heart is implanted in a more anatomical position avoiding enlarged atria. A separate end-to-end anastomoses of the caval veins are performed. And a bicaval anastomosis of donor and recipient inferior vena cava (IVC) and superior vena cava (SVC) is performed. The bicaval technique has been further refined by the addition of a bipulmonary vein technique whereby common cuffs of the pulmonary veins are left in place" (Lerret & Stendahl, 2017, p. 741).

PHYSIOLOGY OF THE TRANSPLANTED HEART

The physiology of the transplanted heart is distinctive. Both the recipient and donor atria are present, but function separately, resulting in decreased atrial input. The transplanted heart does not experience angina because of denervation. Low cardiac output can result, as the transplanted heart has no innervation pacing the heartbeat.

Postoperative Management

Care of the heart transplant patient is similar to that for any other cardiac surgery. Good perfusion with adequate gas exchange and hemodynamic stability are goals after transplantation. Normal perfusion is evidenced by normalized blood gases, adequate urinary output, and adequate blood pressure.

Emergency Alert: A major complication from surgery is hemorrhage. This can be due to anticoagulation therapy secondary to end-stage heart disease, reoperation (prior cardiac surgery), and cardiopulmonary bypass during surgery, or clotting related to hepatic congestion secondary to severe right heart failure. The donor heart is smaller than the diseased heart it replaced. This results in the pericardial space acting as a reservoir for blood, resulting in cardiac tamponade. Frequent milking of the chest tubes helps decrease the blood volume in the pericardial space and maintains the patency of the chest tubes.

"Some of the early complications after heart transplant in children include low cardiac output, systemic hypertension, pulmonary hypertension and post-operative tachy- and brady-arrhythmias.

Infections are a leading cause of death and morbidity in the first year following pediatric heart transplantation. Most severe infections occur during the initial hospitalization" (Webber, 2014, pp. 1412–1413). Meticulous care of IV, central lines, arterial lines, dressings, drains, and catheters is observed in the intensive care units to prevent infections.

RENAL TRANSPLANTATION IN INFANTS AND CHILDREN

Renal transplantation in infants and children has been the most successful of all types of transplants. Recent advances in the techniques of dialysis and the management of end-stage renal disease (ESRD) in neonates have allowed many patients with complex urologic or hereditary abnormalities to reach the age and size at which transplantation is possible. These advances have permitted the implementation of renal transplantation, along with dialysis, as a complementary treatment in the care of infants with irreversible renal dysfunction.

Etiology

Acute renal failure in infants is most often the consequence of hemodynamic instability, hypoxia, or malperfusion, resulting in acute tubular necrosis. Most of these infants either recover sufficient function for normal long-term survival or die of multisystem failure. Chronic renal failure is uncommon in infants. Congenital nephrosis, dysplasia/hypoplasia, and other anatomic abnormalities associated with complex urogenital malformations are the common causes of ESRD in infants.

In children younger than 5 years of age with glomerulonephritis, 46% have a congenital cause for ESRD. Lupus nephritis and recurrent pyelonephritis, which are more common in older patients, are uncommon causes of ESRD in the infant. Hereditary causes of renal failure are important to identify in planning the appropriate overall treatment strategy; evaluation of other family members and provision of genetic counseling, when needed, must also be considered. Appropriate identification of the cause of the ESRD also allows assessment of the potential for recurrence within a transplant allograft and consideration of living related–donor transplantation.

"Infants with ESKD (end-stage kidney disease) during the first year of life may suffer neurologic abnormalities. These include alterations in mental function, neurocognitive delay, microcephaly, and involuntary motor phenomena, such as myoclonus, cerebellar ataxia, tremors, seizures, and hypotonia. The pathogenesis is unclear, although aluminum toxicity, uremia, prematurity, hypertensive crises, and dialysis-related seizures have been incriminated" (Chambers, Pearl, & Ettenger, 2017, p. 468).

According to the OPTN National Data, the number of kidney transplants performed in the United States on children less than 1 year of age from January 1, 1988 to April 30, 2019 is 116. The number of children aged 1 to 5 years is impressively higher at 4,552 compared to the younger recipients (OPTN, 2019a).

Based on the 2016 OPTN/SRTR annual report, 917 pediatric candidates were added to the kidney transplant waiting list, 522 (57%) as inactive. The number of prevalent pediatric candidates (listed at age less than 18 years and on the list on December 31 of the given year) has been steadily increasing and reached 1,494 on December 31, 2016. The most common reason for inactive status among newly listed candidates in 2016 was incomplete workup (52.1%), followed by living donor candidate status (16.8%), and too well to need transplant (11.6%). Over the past decade, the age of pediatric candidates on the list at year-end shifted, with an increase in those aged 1 to 5 years (14.9%–24.6%) and a decrease in those aged 11 to 17 years (66.3%–54.3%). Proportions of candidates with congenital anomalies of the kidney and urinary tract (CAKUT) as primary cause of disease increased from 27.8% in 2006 to 37.3% in 2016, and proportions with glomerulonephritis decreased from 12.3% to 7.1%. Most candidates (65.7%) had a calculated panel reactive antibodies (cPRA) of less than 1% (Hart et al., 2018).

"The most common primary diagnosis remain aplastic, hypoplastic, or dysplastic kidney and obstructive uropathy, each present in about 15% of patients. FSGS (focal segmental glomerulosclerosis) is the third most common (12%) and continues to be the most prevalent acquired renal disease" (Chambers et al., 2017, p. 453).

Pretransplant Management

Pretransplant tests are done to evaluate the patient's physical status and also to identify potential problems. The tests help determine whether transplantation is truly the best option and will increase the likelihood of success. Transplant feasibility consists of histocompatibility laboratory tests of tissue typing, panel reactive antibody, cross-match testing, and blood typing.

Dialysis is often used to keep the child stable until a donor is available or the child reaches at least 10 kg (Chambers et al., 2017). "At some centers, transplantation has been successful in children who weighed less than 10 kg and who were younger than 6 months" (Chambers et al., 2017, p. 455).

Kidney Transplant Surgery

Kidney transplantation in very small recipients can be very challenging due to the size of the recipient versus the size of the donor kidney. The size of the graft can impact anastomosis time, ischemia time, and may eventually cause early graft dysfunction. In infants or small children, the placement of the donor graft is done intra-abdominally. The aorta and inferior vena cava are among the vessels most commonly used, as they are larger with higher blood (Chambers et al., 2017).

Dialysis

Dialysis is indicated in infants as in older children if complications of medical management of ESRD occur, namely, hyperkalemia, volume overload, acidosis, intractable hypertension, or uremic symptoms, such as vomiting. Dialysis can be accomplished by hemodialysis or peritoneal dialysis. Dialysis centers can take older children until a transplant is available. In neonates and small children, peritoneal dialysis is frequently utilized because (1) it avoids the multiple transfusions associated with hemodialysis; (2) it allows smoother gradual correction of electrolyte abnormalities, preventing cerebral disequilibrium syndrome in small infants; and (3) it is easier to perform. For long-term peritoneal dialysis, parents are taught how to care for the infant. This allows the parent to take the child home and be a family. The infant is given time to

grow and normalize as much as possible. Glucose and electrolytes can be enhanced via peritoneal dialysis to enhance nutrition.

Nutritional Support

Nutritional support is a primary concern for the renal patient. Growth retardation is a major problem. The cause of this growth disturbance is multifactorial and includes both protein and calorie insufficiency, renal osteodystrophy, aluminum toxicity, acidosis, impaired somatomedin activity, and insulin resistance. A registered dietitian will need to constantly monitor the nutritional needs of the infant and child. The most intense period of growth occurs during the first 2 years of life. Head circumference is the key to monitoring growth, as it follows overall body development. When a child experiences uremia, feeding and nutritional support may be difficult. To promote optimal nutrition, use of enteral feeding tubes is sometimes necessary, especially if dialysis is being used (Chambers et al., 2017).

INTESTINAL TRANSPLANT

According to the OPTN National Data, the number of intestinal transplants performed in the United States on patients less than 1 year of age from the year 1990 to 2019 is 311. The number of patients 1 to 5 years of age is 874 from the year 1990 to 2019 (OPTN, 2019a).

Since 1985, data compiled by the international Intestinal Transplant Registry show that 55 intestinal transplant programs have performed 601 transplants, of which 402 were in children. Although not many infants and children have had intestinal transplants, the numbers are growing.

Intestinal transplantation is an acceptable treatment for patients with intestinal failure according to Centers for Medicare and Medicaid Services (CMS; Reyes, 2014). One-year survival rates are nearly 90% (OPTN, 2019a). For pediatric intestine recipients, 1- and 5-year survival rates are 86.2% and 75.4%, respectively (Smith et al., 2019; U.S. Department of Health & Human Services, 2017).

Intestinal Transplant Considerations

"Intestinal failure (IF) is now defined as the inability of the functional intestinal mass to provide adequate nutrition and hydration to maintain normal growth and development, and to support life. IF (intestinal failure) can occur exclusive of intestinal length" (Mangus & Subbarao, 2013, p. 162).

Patients with poor intestinal function who cannot be maintained on TPN via IV routes are potential candidates for transplantation. In some patients, most of the bowel has been surgically removed to treat the disease, or it became diseased. This produces the short-gut syndrome, which is the most common cause of intestinal failure. For some infants and children, the entire intestine is present, but it is unable to absorb enough fluids and nutrients. Transplantation is a potentially lifesaving option for patients with intestinal failure who cannot tolerate TPN. Because patients' survival rates are better after isolated bowel transplants, this is the preferred type of transplant. Combined intestinal–liver transplants or cluster transplants are options for patients who have developed liver failure on TPN or for patients who have large, local tumors that can only be removed by removing several organs.

Diseases leading to intestinal transplantation include the following:

- Short-gut syndrome caused by volvulus, gastroschisis, trauma, necrotizing enterocolitis (NEC), ischemia, Crohn's disease
- Poor absorption caused by microvillus inclusion, secretory diarrhea, autoimmune enteritis
- Poor motility caused by pseudo-obstruction, aganglionosis (Hirschprung's disease), visceral neuropathy
- Tumor or cancer such as desmoid tumor, familial polyposis (Gardner's disease)
- Congenital intestinal atresia
- Poor intestinal absorption
- Autoimmune disorders
- Brush-border element assembly problems
- Microvillus inclusion disease
- Severe disorders of motility resulting from intestinal pseudo-obstruction (congenital or acquired)
- Gardner's disease (intestinal polyposis)
- Serious complications of TPN therapy
- Thrombosis (blockage due to a blood clot) of two or more major central veins (subclavian, jugular, femoral)
- Repeated episodes of line sepsis or line infections
- The decision to proceed with intestinal transplantation is made only after careful evaluation determines that surgery is the child's most promising treatment option.

Donor Options

Most intestinal grafts come from cadaver donors—people who have been declared dead in a hospital while attached to a ventilator (artificial breathing machine). Consent is given by the next of kin for organ removal and transplant. Occasionally, a portion of the bowel is taken from a living donor—a relative such as a parent or sibling.

The graft used depends on the patient's condition, including the viability of the remaining bowel (Reyes, 2014). For the patient experiencing problems with the liver and intestine, determination of the course of treatment including the surgical procedure such as simultaneous hepatic and intestinal replacement depends on the physical condition of the patient. If portal hypertension is severe, or there are coagulopathy problems, jaundice, and cholestasis then simultaneous transplants may be necessary (Reyes, 2014).

Intestinal Transplant Evaluation

Small intestine transplant evaluation is similar to liver transplant evaluation. It is important that the child has a good history of central-line placement, IV access, upper gastrointestinal studies, number of gastrointestinal resections, and length of bowel to ensure that transplantation is the best medical option.

Studies done for evaluation include the following:

- Blood tests
- Chemistry panel
- Liver panel
- Hematology group
- Coagulation studies
- Blood typing and antibody screen
- Infectious diseases: hepatitis B, hepatitis C, HIV, cytomegalovirus, Epstein–Barr virus
- Imaging studies and other tests
- Ultrasound of the liver in combined intestinal–liver transplants
- CT scan
- MRI to map abdominal vasculature
- Endoscopy (esophagogastroduodenoscopy, EGD)
- Mobility studies
- Colonoscopy
- Liver biopsy for combined liver–intestinal patients to determine whether TPN damage is reversible
- Psychosocial and developmental evaluations
- Social worker
- Child development expert evaluation

If the child is a candidate for intestinal transplantation, his or her name is added to the transplant waiting list for an isolated intestinal transplant or for a combined liver and intestinal transplant based on the severity of organ damage and dysfunction. Transplant waiting lists are maintained by the UNOS (OPTN, 2012).

Postoperative Management

After the procedure, patients are placed on immunosuppressive drugs to prevent rejection of the transplanted organ. The doctors perform biopsies (take tissue samples of the intestine) at various intervals to check for signs of rejection. Rejection may be managed by adding immunosuppressive drugs or increasing dosages. Patients who have received intestinal transplants remain on immunosuppressive drugs indefinitely. Since patients on immunosuppressive drugs are vulnerable to infections by bacteria and viruses, they are monitored for signs and symptoms of infection. Particular attention is paid to wound care issues and fluid management. A multidisciplinary team performs a nutritional assessment to determine the child's caloric needs.

Reyes (2014) states that "endoscopic surveillance of the graft with biopsy remains the gold standard of intestine graft evaluation; this is performed weekly for the first 3 to 4 weeks, then at gradually decreasing frequencies depending on clinical need" (p. 1320).

Enteral feedings are started as soon as possible gradually weaning off TPN (Reyes, 2014). Oral aversion is common. So feeding may be a challenge in this population.

Intestinal Transplantation Survival

Improved antirejection drugs, refined surgical procedures, and a greater understanding of immunology have contributed to successful intestinal transplants. Short-term survival is now comparable to lung transplantation results. Most of the patients in the international Intestinal Transplant Registry have been followed for a brief time; it will take several years to obtain reliable data on long-term results (Intestinal Transplant Registry, 2005).

Until a few years ago, cyclosporine was used most often to prevent organ rejection. Tacrolimus (Prograf, Astellas Pharma US, Deerfield, IL) has been given to most intestinal transplant patients over the past 4 years. As of June 1995, 49% of all intestinal patients had died, usually from sepsis (42%) or multiple organ system failure (30%). Four patients (5%) died of rejection. Of the surviving patients, 78% had stopped TPN and had resumed a normal, oral diet.

To become the standard treatment for intestinal failure, transplantation must offer better survival, better quality of life, and lower costs than TPN. Considerable progress has been made toward these goals, but further refinements are needed before bowel transplantation becomes a routine surgical procedure.

Despite improved immunosuppression, the intestine offers more rejection than other organs.

Rejection of the intestine is also difficult to diagnose, as there are no biochemical (blood) tests to indicate rejection. To prevent intestinal rejection, patients require higher doses of immunosuppression than with other types of transplantation. Now, because of new, more specific antirejection medications, the success of intestinal transplant has improved dramatically (Intestinal Transplant Registry, 2005).

ORGAN PROCUREMENT

Organ procurement is facilitated by the UNOS, a nonprofit, scientific, and educational organization that administers the nation's only OPTN and was established by the U.S. Congress in 1984. Functions of OPTN include the following:

- Collects and manages data about every transplant event occurring in the United States
- Facilitates organ matching and placement process using UNOS-developed data technology and the UNOS Organ Center
- Brings together medical professionals, transplant recipients, and donor families to develop organ transplantation policy

UNOS was awarded the initial OPTN contract on September 30, 1986. UNOS is the only organization to ever manage the OPTN and has continued to administer the contract for more than 16 years and four successive contract renewals (OPTN, 2012).

Waiting List

The OPTN maintains the only national patient waiting list and features the most comprehensive data available in any single field of medicine (OPTN). UNetSM is the web-based electronic utility used by the contractor to conduct the business of OPTN. UNetSM comprises the Match System, all software, applications, and security architecture needed for the collection, modification, validation, reporting, management, and redundancy of data associated with the tasks and activities of the OPTN. The Organ Procurement Organization, having identified a potential organ donor, assumes responsibility for donor management and organ allocation. The Match System is the computerized algorithm used to prioritize candidates waiting for organs. It eliminates potential recipients whose size or ABO type is incompatible with that of a donor, and then ranks those remaining potential recipients according to the ranking system (OPTN, 2012).

The waiting list is the computerized list of candidates waiting to be matched with specific donor organs in hopes of receiving transplants. Candidates are registered on the waiting list by member transplant centers. The candidate's transplant program is responsible for ensuring the accuracy of candidate ABO blood group system data on the waiting list. Each transplant program implements and operates procedures for online verification of a candidate's ABO data on the waiting list against the source documents by an individual. The transplant program maintains records documenting separate verification of the source documents against the entered ABO data. Upon entry of the candidate's wait-list data, the candidate will be added to the wait-list but will not be listed as an active candidate until separate verification of the candidate's ABO data has taken place (OPTN policy 3. 2019).

All transplant candidate interactions will be required to be completed through UNetSM by transplant programs. The Organ Center will facilitate candidate listings and modifications in the event of computer and/or Internet failure. When the Organ Center facilitates a candidate's listing or modification due to computer and/or Internet failure, the transplant center will be required to submit a statement explaining the event.

Each transplant candidate must be ABO typed on two separate occasions prior to listing. Two separate occasions are defined as two samples, taken at different times, sent to the same or different laboratories. Transplant candidates are listed on UNetSM with the candidate's actual blood type (OPTN, 2012).

PEDIATRIC CRITICAL PATHWAY

After brain death has been declared, and consent granted for organ donation, pediatric specialists and organ procurement professionals should work together to care for the organ donor and family members. The UNOS (2005; Table 27.2) describes optimal care for the pediatric organ donor and maps the process to improve the outcome for successful organ transplantation.

TABLE 27.2

CRITICAL PATHWAY FOR DONATION AFTER CARDIAC DEATH

Collaborative Practice	Phase I Identification and Referral	Phase II Preliminary Evaluation	Phase III Family Discussion and Consent	Phase IV Comprehensive Evaluation and Donor Management	Phase V Withdrawal of Support/ Pronouncement of Death/Organ Recovery
The following health care professionals may be involved in the Donation After Cardiac Death (DCD) donation process: Check all that apply: ❍ Physician (MD) ❍ Critical Care RN ❍ Nurse Supervisor ❍ Medical Examiner/ Coroner ❍ Respiratory Therapy (RT) ❍ Laboratory ❍ Pharmacy ❍ Radiology ❍ Anesthesiology ❍ OR/Surgery Staff ❍ Clergy ❍ Social Worker ❍ Organ Procurement Coordinator (OPC) ❍ Organ Procurement Organization (OPO)	Prior to withdrawing life support, contact local OPO for any patient who fulfills the following criteria: ❍ Devastating neurologic injury and/or other organ failure requiring mechanical ventilatory or circulatory support ❍ Family and/or care giving team initiate conversation about withdrawal of support Following referral, additional evaluation is done collaboratively to determine if death is likely to occur within 1 hour (or within a specified timeframe as determined by care giving team and OPO) following withdrawal of support Patient conditions might include the following: ❍ **Ventilator dependent for respiratory insufficiency:** apneic or severe hypopneic; tachypnea ≥ 30 breaths/ min after DC ventilator ❍ **Dependent on**	Physician ❍ Supportive of withdrawal of care and has communicated grave prognosis to family ❍ Review DCD procedure with OPC ❍ Will be involved in withdrawal/ pronouncement ❍ Will designate a person to be involved with withdrawal and/or pronouncement Family ❍ Has received grave prognosis ❍ Understands prognosis ❍ In conjunction with care giving team, decide to withdraw support Patient ❍ Age _____ ❍ Weight _____ ❍ Height _____ ❍ ABO _____ ❍ Medical Hx _____ ❍ Surgical Hx _____ ❍ Social Hx _____ ❍ Death likely < 1 hour following withdrawal (determined collaboratively by	❍ Support services offered to family ❍ OPC/hospital staff approach family about donation options ❍ Legal next-of-kin (NOK) fully informed of donation options and recovery procedures ❍ Legal NOK grants consent for DCD following withdrawal of support ❍ Family offered opportunity to be present during withdrawal of support ❍ OPC obtains _____ Witnessed consent from legal NOK for DCD _____ Signed consent Time _____ Date _____ _____ Detailed med/soc history Notification of donation ❍ Hospital supervisor ❍ ME/coroner notified _____ ME/coroner and releases for donation _____ ME/coroner has restrictions	❍ MD, in collaboration with OPO, implements management guidelines ❍ Establish location and time of withdrawal of support ❍ Review plan for withdrawal to include: – Pronouncing MD (should be in attendance for duration of withdrawal of support, determination of death, and may not be a member of the transplant team) – Comfort care – Extubation and discontinuation of ventilator support – Establish plan for continued supportive care if pt survives > 1 hour or predetermined time interval after withdrawal of support ❍ Notify OR/Anesthesia _____ Review patient's clinical course, withdrawal plan, and potential organ recovery	❍ Withdrawal occurs in _____OR _____ICU _____Other_____ ❍ Family present for withdrawal of support _____ Yes _____ No ❍ OR/room prepared and equipment set up ❍ Transplant team in the OR (not in attendance during withdrawal) ❍ Care giving team present ❍ Administration of preapproved medication (e.g., heparin/Regitine) ❍ **Withdrawal of support according to hospital/MD practice guidelines** **Time** _____ **Date** _____ ❍ **Vital signs are monitored and recorded every minute (see attached sheet)** ❍ **Pt pronounced dead and appropriate documentation completed**

(*continued*)

TABLE 27.2

CRITICAL PATHWAY FOR DONATION AFTER CARDIAC DEATH (*continued*)

Collaborative Practice	Phase I Identification and Referral	Phase II Preliminary Evaluation	Phase III Family Discussion and Consent	Phase IV Comprehensive Evaluation and Donor Management	Phase V Withdrawal of Support/ Pronouncement of Death/Organ Recovery
	mechanical circulatory support: LVAD; RVAD; V-A ECMO; pacemaker with unassisted rhythm < 30 beats/min ❍ **Severe disruption in oxygenation:** PEEP ≥ 10 and SaO_2 ≤ 92%; FiO_2 ≥0.50 and SaO_2 ≤ 92%; V-V ECMO requirement ❍ **Dependent upon pharmacologic circulatory assist:** norephinephrine, epinephrine, or phenylephrine ≥ 0.2 mcg/kg/min; dopamine ≥ 15 mcg/kg/min ❍ **IABP and inotropic support:** IABP 1:1 and dobutamine or dopamine ≥ 10 mcg/kg/min and CI ≤ 2.2 L/min/M^2; IABP 1:1 and CI ≤ 1.5 L/min/M^2	evaluating injury, level of support, respiratory drive assessment)	*Stop pathway if –* ❍ *Family, ME/coroner denies consent* ❍ *Patient determined to be unsuitable candidate for DCD* ❍ *Patient progresses to brain death during evaluation — refer to brain dead pathway*	procedures _____ Schedule OR time ❍ Notify recovery teams ❍ Prepare patient for transport to prearranged area for withdrawal of support ❍ Patient transported to prearranged area ❍ Note: Should the clinical situation require premortum femoral cannulation, the following should be reviewed: – Family consent or understanding – MD inserting cannula – Time and location of cannula insertion – If death does not occur, determine if cannula should be removed	**Time** _____ **Date** _____ **MD** _____ ❍ **Transplant team initiates surgical recovery** at prescribed time following pronouncement of death ❍ Allocation of organs per OPTN/UNOS policy ❍ ***If cardiac death not established within 1 hour or predetermined time interval after withdrawal of support – Stop pathway Patient moved to predetermined area for continuation of supportive care*** ❍ *Postmortem care administered*
Labs/Diagnostics		❍ ABO ❍ Electrolytes ❍ LFTs ❍ PT/PTT ❍ CBC with Diff ❍ Beta HCG (female pts) ❍ ABG		Repeat full panel of labs additionally: ❍ Serology testing ❍ Infectious disease profile ❍ Blood cultures X2 ❍ UA and urine culture ❍ Sputum culture ❍ Tissue typing	
Respiratory	❍ Maintain ventilator support ❍ Pulmonary toilet PRN	❍ Respiratory drive assessment RR _____ VT _____ VE_____ NIF _____	❍ ABGs as requested ❍ Notify RT of location and time of withdrawal of support	❍ Transport with mechanical ventilation using lowest FiO_2 possible while maintaining the SaO_2 > 90%	

(*continued*)

TABLE 27.2

CRITICAL PATHWAY FOR DONATION AFTER CARDIAC DEATH (*continued*)

Collaborative Practice	Phase I Identification and Referral	Phase II Preliminary Evaluation	Phase III Family Discussion and Consent	Phase IV Comprehensive Evaluation and Donor Management	Phase V Withdrawal of Support/ Pronouncement of Death/Organ Recovery
		Minutes off ventilator ___ ❍ Hemodynamics while off ventilator → HR _____ BP _____ SaO_2 _____			→
Treatments/Ongoing Care	Maintain standard nursing care to include: → ❍ Vital signs q 1 hour ❍ I and O q 1 hour				❍ Postmortem care at conclusion of case
Medications				❍ Provide medications as directed by MD in consult OPC	❍ Heparin and other medications prior to withdrawal of support
Optimal Outcomes	The potential DCD donor is identified, and a referral is made to the OPO	The donor is evaluated and found to be a suitable candidate for donation	The family is offered the option of donation, and their decision is supported	Optimal organ function is maintained, withdrawal of support plan is established, and personnel are prepared for potential organ recovery	Death occurs within 1 hour of withdrawal of support and all suitable organs and tissues are recovered for transplant

ABG, arterial blood gas; BP, blood pressure; CBC, complete blood count; ECMO, extracorporeal membrane oxygenation; HCG, human chorionic gonadotropin; IABP, Intra-Aorta balloon pump; LVAD, left ventricular assist device; NIF, negative inspiratory force; OPTN, organ procurement and transplantation network; PEEP, positive end expiratory pressure; PTT, partial Thromboplastin time; RR, respiratory rate; RVAD, right ventricular assist device;UNOS, united network for organ sharing; VE, volume exhaled; VT, ventricular tachycardia.

Note: Shaded areas indicate Organ Procurement Coordinator (OPC) Activities

Source: Adapted from United Network for Organ Sharing. (2002). *Critical pathway for the organ donor.* Retrieved from https://www.unos.org/wp-content/uploads/unos/Critical_Pathway.pdf

STEM CELL TRANSPLANTATION

Human umbilical cord blood (CB) in recent years has become a source of hematopoietic progenitor cells. These so-called stem cells are used to treat a variety of diseases such as malignancies, hemoglobinopathies, immunodeficiencies, and inborn errors of metabolism.

Umbilical CB was used until recently to assess infants' health status. Otherwise, CB was discarded with all the other biologic tissues of birth: placenta, amniotic fluid, birth sac, and umbilical cord. These biologic tissues have been shown to be useful medically for other purposes. For example, it was found that a specific lung lipid isolated from amniotic fluid could ascertain the lung maturity of the fetus in the last trimester of pregnancy: the lecithin/sphingomyelin ratio.

Physiology

Umbilical CB is extremely rich in stem cells. Stem cells differ from other kinds of cells in the body. Regardless of their source, they have three general properties:

1. They are capable of dividing and renewing themselves for long periods.
2. The cells are unspecialized.
3. They give rise to specialized cells.

There is controversy regarding where stem cells and progenitor cells originate in the yolk sac or aorta-gonad-mesonephros region/intraembryonic splanchnopleural region. Cells move through the fetal liver and then the fetal circulation, where the numbers are high at birth.

In October 1988, the first CB transfusion was performed for a patient with Fanconi anemia: a sibling donor contributed the HLA-matched cells. Since then, several diseases have been treated with stem cells. In a number of genetic, hematologic, and oncologic disorders, infusion of CB can be a potentially lifesaving procedure. Allogenic (related or unrelated) or autologous (self) bone marrow is the usual source of hematopoietic progenitor cells. One child in 2,700 might eventually benefit from an autologous stem cell transplant. Bone marrow is not always readily available. Umbilical CB can be a viable alternative for certain conditions (Table 27.3).

Collection of Cord Blood

CB can be collected from the placenta in situ during the third stage of labor or immediately after delivery of the placenta. About 50% to 70% of donated units are ineligible for storage, mainly because of low volume. Each unit should contain more than 40 mL of CB for a child weighing up to 30 kg. Maximal storage time is unknown, but, under stable conditions, the cells are likely to remain viable for decades.

CB is collected according to directions from the particular bank. In general, the samples are obtained from normal full-term deliveries under orders from the healthcare provider (physician, midwife, or nurse practitioner). Once labor has been established, the nurse will label the tubes, place them in a plastic zip-closure bag, and return them to the kit's Styrofoam box per instructions. The Styrofoam box will then be labeled with time, date, name, and initials of collector. The tops of the heparin vials are cleansed with alcohol and 5 mL is drawn. The heparin is injected into 60-mL syringes. Each syringe is labeled.

After the infant's birth, CB is collected within 10 minutes. It is drawn from the umbilical vein with as much blood as possible. The syringes are inverted back and forth for 1 to 2 minutes to mix the blood and heparin well. The syringes are capped and put into the provided plastic bag. Then they are packaged into the Styrofoam box with the provided absorbent pad. Blood should remain at room temperature to ensure viability of stem cells. CB is not refrigerated. It is usually the families' responsibility to ship the blood in a timely manner to the CB bank.

TABLE 27.3

CONDITIONS FOR WHICH UMBILICAL CORD BLOOD CAN BE A VIABLE ALTERNATIVE

Disease	Indication	Blood Cell Transplantation
Leukemia, lymphomas	Engraftment of healthy cells	Effective
Bone and soft tissue sarcomas, Wilms' tumor, brain tumors	Very rarely indicated	Effectiveness unproven
Hematologic diseases	The new donor cells will produce normal white cells, red cells, and platelets	Effective
Immunodeficiency diseases	Engraftment of healthy allogenic cells	Effective
Hemoglobinopathies	The new donor cells will produce normal white cells, red cells, and platelets	Effective
Metabolic storage disorders	Donor cell will eventually produce the deficient enzyme	Controversial; may be effective in select patients
Genetic conditions	Cells from umbilical cord blood can be isolated, transduced, and engrafted to produce mature hematopoietic and lymphoid cells for at least several years	Effective in select diseases

Sources: Adapted from Baggott, C., Kelly, K., Fochtman, D., & Foley, G. (Eds.). (2002). *Nursing care of children and adolescents with cancer* (3rd ed.). Philadelphia, PA: Saunders; and Hockenberry-Eaton, M. J. (Ed.). (1998). *Essentials of pediatric oncology nursing: A core curriculum.* Glenview, IL: Association of Pediatric Oncology Nurses.

Cord Blood Banks

Private banks such as the Cord Blood Registry in San Bruno, California, offer collection kits to families. Private banks are companies that are accredited by the American Association of Blood Banks (AABB). Typical fees range from $1,000 to $1,500 for registration and collection. Storage is charged $100 a year, but there are no additional fees for retrieving the cells for use. The costs are borne by the families.

Public cord banks accept collections only from affiliated hospitals. Units stored in them are available for any patient in need who

is medically eligible for transplantation therapy. In the unlikely event that the donor or a member of his family develops an indication for a stem cell transplant, the stored cells could be traced and used. Public CB banks charge no fees for donation, but may charge $15,000 or more if the blood is actually used. The number of public banks is limited.

The American Academy of Pediatrics (Shearer et al., 2017) recommends that institutions or organizations (private or public) involved in CB banking should consider the following recommendations:

- Recruitment practices should be developed with an awareness of the possible emotional vulnerability of pregnant women and their families and friends. Efforts should be made to minimize the effect of this vulnerability on recruitment decisions.
- Accurate information about the potential benefits and limitations of allogenic and autologous CB banking and transplantation should be provided.
- A policy should be developed regarding disclosing to the parents any abnormal findings in the harvested blood.
- Specific permission for maintaining demographic medical information should be obtained, and the potential risks of breaches of confidentiality disclosed.
- Written permission should be obtained during prenatal care, and before the onset of labor. The practice of collecting blood first and obtaining permission afterward is considered unethical and should be discouraged.
- Consultation with the institutional review board or hospital ethics committee about recruitment strategies and the wording of consent forms is recommended.
- CB collection should not be done in complicated deliveries, and the CB stem collection program should not alter routine practice for the timing of umbilical cord clamping.
- Because of the investigational status of CB banking and the high risk for its potential abuse, the regulatory agencies (e.g., U.S. Food and Drug Administration, Federal Trade Commission, state equivalent of these federal agencies) are encouraged to have an active role in providing oversight for the safety and welfare of the population (Ikuta, 2008; Shearer et al., 2017).

Cord Blood Transfusion in Neonate

There are two types of cord stem cell transfusions: frozen and fresh. Each type of transfusion is discussed in regard to considerations, side effects, and nursing care needed for the neonate.

Frozen stem cells are used in autologous (collected from the patient) CB transplants. A preservative, dimethyl sulfoxide (DMSO) is added to the cells just prior to cryopreservation. It acts to coat the cells and prevent their lysis during the process of freezing and thawing. DMSO is infused to the patient with the transfusion of the cells. The garlic-like odor of DMSO is very distinctive and unpleasant. DMSO is excreted primarily through the respiratory system. DMSO is smelled and tasted as soon as it is infused, which can result in the baby having nausea and vomiting. Other side effects commonly seen are bradycardia and shortness of breath. Volume overload can occur as each bag of cells contains 50 to 100 mL. Hypertension may require medication with antihypertensives and diuretics. Giving the transfusion over a 2 to 4–hour time period and in two different sessions may help lessen side effects. A significant reaction to DMSO may occur even without volume overload. The transfusion is thawed to break the ice crystals, so it is advised to keep the infant's environment as thermally neutral as possible with the use of a radiant warmer, isolette, or warm blankets. Monitor the temperature frequently. Stem cells should not be warmed as they may be damaged. After the transfusion, red urine may be seen as some of the cells will be excreted in the urine. Red urine will diminish over time. Hydration should be provided following infusion.

Fresh stem cells are given for allogenic transplants (related or unrelated) within 48 hours of collection. **Emergency Alert: Side effects may include hemolytic transfusion reactions, volume overload, pulmonary microemboli, and infection (as the transfusion is neither irradiated nor filtered).**

Assess the family's understanding of CB transfusion prior to the procedure and provide information and/or education. **Quality and Safety: For either transfusion type, careful monitoring of intake and output, oxygenation saturation, heart and respiratory rates, and blood pressures is warranted.** Vital signs are taken before, during, and after the infusion. Interventions are based on the type of transfusion used (Table 27.4).

TABLE 27.4

POSSIBLE COMPLICATION SEQUENCE FOR CORD BLOOD TRANSFUSION

Immediate	Delayed (First Month)	Late Effects (After First Month)
Nausea/ vomiting	Bone marrow suppression	Immunosuppression
Diarrhea	Mucositis	Chronic graft-versus-host disease
Red urine	Hemorrhagic cystitis	Cataracts
Parotitis	Anorexia	Endocrine dysfunction
Hypertension	Capillary leak syndrome	Pulmonary restrictive disease
Volume overload	Veno-occlusive disease	Genetic disease recurrence
Apnea/ bradycardia	Graft failure	Secondary malignancies
Tachypnea	Graft-versus-host disease	Bacterial infections
Respiratory distress	Acute renal failure	Cytomegalovirus infection
	Bacterial infection	Varicella zoster infection
	Viral infections (herpes simplex, cytomegalovirus)	Latent viral infections
	Fungal infection	*Pneumocystis carinii* pneumonia

Sources: Adapted from Baggott, C., Kelly, K., Fochtman, D., & Foley, G. (Eds.). (2002). *Nursing care of children and adolescents with cancer* (3rd ed.). Philadelphia, PA: Saunders; Hockenberry-Eaton, M. J. (Ed.). (1998). *Essentials of pediatric oncology nursing: A core curriculum.* Glenview, IL: Association of Pediatric Oncology Nurses.

TABLE 27.5

ADVANTAGES AND DISADVANTAGES OF CORD BLOOD TRANSFUSION

Advantages	Disadvantages
1. Easily obtained from cord at delivery of child. Not a good source of progenitor cells.	1. Can only be obtained at delivery if it is matched perfectly. Procedure for obtaining cord blood must be followed exactly. At times, not enough is collected or cannot be collected due to difficult delivery.
2. Can use unmatched cord blood from donors.	2. Need adequate volume of cord blood.
3. Decreased graft-versus-host disease with use of cord blood.	3. Slower engraftment of cells and delayed rebuilding of immune system, depending on hospital criteria for discharge, could mean greater length of stay.
4. Infection risk from blood-borne viruses lessened.	4. At risk longer from infection due to delayed rebuilding of immune system.

Umbilical CB transfusions offer hope to families of infants with various diseases requiring hematopoietic progenitor cells. It is not a common procedure as yet. In neonatal units affiliated with CB banks, study of benefits versus ineffectiveness is occurring. It is still an uncommon procedure that can have far-reaching consequences. Thorough education of the family is required to deal with potential complications associated with stem cell infusion. Neonatal nurses need to be aware of the immediate, delayed, and late effects to give prompt intervention and treatment as needed. Advantages and disadvantages of CB transfusion are listed in Table 27.5.

SUMMARY

In the past decade, transplantation has become more common but is more the exception than the rule. Transplants with solid organs were the mainstay, but stem cell transplants are beginning to be explored. Transplants are a tertiary treatment that is not irreversible. It is the last, best option for many patients. The next few years will change indications for transplant, with earlier treatments and procedures.

CASE STUDY

■ **Identification of Problem.** Late preterm twin female infants born vaginally; presented with lethargy, poor feeding, and weight loss at 3 days of age.

■ **Assessment: History and Physical Examination.** Twin female late preterm infants were delivered vaginally to a 28-year-old G2 P2 woman after an uncomplicated pregnancy. Infants were 36 weeks' postmenstrual age with twin A's birth weight of 2.8 kg and twin B's birth weight of 2.7 kg. Twin A had Apgars of 9^1 9^5 and twin B had Apgars of 8^1 9^5. Admission to the NICU. Both infants had a gross normal physical examination upon admission. As late preterm infants, they had temperature instability requiring warming in isolettes. They are poor nipplers who require gavage feeds.

■ **Second Day of Life.** Newborn screens were sent on the second day of life. Screens are sent overnight for spectronomy.

■ **Differential Diagnosis**
1. Late preterm twins
2. Hypothermia
3. Feeding difficulties

■ **Diagnostic Tests.** Newborn screens

■ **Working Diagnosis.** Late preterm twins

■ **Third Day of Life.** These twins were born in a state that has expanded newborn screens. Expanded newborn screening results by spectronomy revealed a rare genetic disorder of methylmalonic acidemia (MMA). In most states, these twins would have died before a diagnosis of MMA would have been made.

■ **Outcome.** The twins are late preterm infants whose appropriate acting masked their metabolic disorder. Both twins were diagnosed with MMA because of expanded newborn screening, which saved their lives. They were put on a low-protein diet and medications until they were big enough for a liver transplant. Liver transplants were done at 15 months of age. Transplants were done early in life to ward against the toxic effects to the brain, kidney, and other organs. They remain on low-protein diets and medications. By having liver transplants, their chances at a long life have improved greatly.

EVIDENCE-BASED PRACTICE BOX

Expanded Newborn Screening

Universal newborn screening is the practice of screening every newborn for genetic testing. Through early identification and treatment, newborn screening improves care. Primary intervention provides an opportunity for reduction in infant morbidity and mortality.

Expanded newborn screening using tandem mass spectrometry (MS/MS) can detect many genetic diseases. Every year, approximately 4 million infants are screened. Of these screened infants, 12,500 are diagnosed with one of the 29 core conditions of the uniform screening panel (Howell et al., 2012). Hearing loss, primary congenital hypothyroidism, cystic fibrosis, sickle cell disease, and medium-chain acyl-CoA dehydrogenase deficiency are the most common genetic entities detected in the United States. A group of experts was assembled in 2006 by the American College of Medical Genetics under the sponsorship of the Health Resources and Services Administration. These experts standardized tests of the expanded newborn screening for the United States. The new expanded screening panel is composed of 29 core conditions. Within the panel are 20 inborn errors of metabolism, three hemoglobinopathies, and six other conditions (Howell et al., 2012).

Many of the diseases of the expanded newborn screen in the past were not diagnosed until after the child was very ill or died. Diagnosing disease early from the newborn screen can result in treatment before mortality or morbidity occurs. In the case of the twin infants with MMA, they had liver transplants to prevent the devastating effects of the disease. Therrell, Buechner, Lloyd-Puryear, van Dyck, and Mann (2008) noted that several studies provide data for the cost-effectiveness of testing. Each infant with detectable disease leads to primary intervention, which leads to cost savings.

False-positive tests have been explored regarding parental stress and anxiety. It was hypothesized that the false-positive tests would cause undue emotional distress in parents and families. Several studies have addressed the false-positive tests and emotional distress of parents/families and concluded that benefits outweighed the distress (Sun, Lam, & Wong, 2012).

The expanded newborn screen has limitations of not enough experts trained to care for neonates affected by complex rare conditions, laboratory capabilities, and possible false-positive results. Long-term follow-up of test results could answer these limitations. While the expanded newborn screen has helped many infants to be diagnosed and cared for earlier, there is still the question of which ones. Consumers need to be educated and empowered to make informed decisions regarding the tests.

References

Howell, R., Terry, S., Tait, V. F., Olney, R., Hinton, C. F., Grosse, S., & Glidewell, J. (2012). CDC grand rounds: Newborn screening and improved outcomes. *Morbidity & Mortality Weekly Report, 61*(21), 390–393. Retrieved from https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6121a2.htm

Sun, A., Lam, C., & Wong, D. A. (2012). Expanded newborn screening for inborn errors of metabolism: Overview and outcomes. *Advances in Pediatrics, 59*, 209–245. doi:10.1016/j.yapd.2012.04.013

Therrell, B. L., Buechner, C., Lloyd-Puryear, M. A., van Dyck, P. C., & Mann, M. Y. (2008). What's new in newborn screening? *Pediatric Health, 2*(4), 411–429. doi:10.2217/17455111.2.4.411

ONLINE RESOURCES

American Society of Transplantation. Retrieved from https://www.myast.org

Boston Children's Hospital Pediatric Transplant Center. Retrieved from http://www.childrenshospital.org/centers-and-services/centers/pediatric-transplant-center

Children's Hospital of Philadelphia (CHOP) Pediatric Transplant Center. Retrieved from https://www.chop.edu/centers-programs/pediatric-transplant-center

Organ Procurement and Transplantation Network. Retrieved from https://optn.transplant.hrsa.gov

The International Society for Heart & Lung Transplantation. Retrieved from http://www.ishlt.org

United Network for Organ Sharing. Retrieved from http://www.unos.org

World Health Organization. (n.d.). Human organ transplantation. Retrieved from https://www.who.int/transplantation/organ/en

REFERENCES

Baggott, C. R., Fochtman, D., Foley, G. V., & Kelly, K. P. (2011). *Nursing care of children and adolescents with cancer* (4th ed.). Philadelphia, PA: Saunders.

Berquist, W., Cox, K., Dyner, L., Enns, G., Esquivel, C., Hurwitz, M., . . . Raganswami, A. (2014). *The pediatric transplant protocols and guide to management of transplant patients*. Stanford Children's Health. Palo Alto, CA: Stanford Children's Health. Retrieved from https://med.stanford.edu/content/dam/sm/peds/documents/Core%20Rotations/green-team/2014liverprotocols%20(2).pdf

Boudi, F. B. (2019). Pediatric liver transplantation. In S. M. Greenstein (Ed.), *Medscape*. Retrieved from https://emedicine.medscape.com/article/1012910-overview

Bucuvalas, J. C., & Feng, S. (2014). Pediatric liver transplantation. In A. D. Kirk, S. J. Knechtle, C. P. Larsen, J. C. Madsen, T. C. Pearson, & S. A. Weber (Eds.), *Textbook of organ transplantation* (1st ed., Vol. 2, pp. 1390–1405). Chichester, England: John Wiley & Sons.

Chambers, E. T., Pearl, M. H., & Ettenger, R. B. (2017). Kidney transplantation in children. In G. Danovitch (Ed.), *Handbook of kidney transplantation* (6th ed., pp. 452–491). Philadelphia, PA: Wolters Kluwer.

Colvin, M., Smith, J. M., Hadley, N., Skeans, M. A., Carrico, R., Uccellini, K., . . . Kasiske, B. L. (2018). OPTN/SRTR 2016 Annual data report: Heart. *American Journal of Transplantation, 18*(Suppl. 1), 291–362. doi:10.1111/ajt.14561

Dhawan, A., & Mieli-Vergani, G. (2005). Acute liver failure in neonates. *Early Human Development, 81*(12), 1005–1010. doi:10.1016/j.earlhumdev.2005.10.003

Di Filippo, S. (2005). Anti-IL-2 receptor antibody vs. polyclonal anti-lymphocyte antibody as induction therapy in pediatric transplantation. *Pediatric Transplantation*, *9*(3), 373–380.

Dumas-Hicks, D., Fitzmorris, F., Cassidy, C., & Canales, K. R. (2017). Transplant complications: Infectious diseases. In S. A. Cupples & S. Lerret (Eds.), *Core curriculum for transplant nurses* (2nd ed., pp. 129–195). Philadelphia, PA: Wolters Kluwer.

Esquivel, C. (2005). *Liver transplantation in children*. Stanford University Medical School. Retrieved from https://www.stanfordchildrens.org/en/service/liver-transplant

Garbade, J., Bittner, H. B., Barten, M. J., & Mohr, F. (2011). Current trends in implantable left ventricular assist devices. *Cardiology Research and Practice, 2011*, 290561. doi:10.4061/2011/290561

Hart, A., Smith, J. M., Skeans, M. A., Gustafson, S. K., Wilk, A. R., Robinson, A., . . . Israni, A. K. (2018). OPTN/SRTR 2016 Annual data report: Kidney. *American Journal of Transplantation, 18*(S1), 18–113. doi:10.1111/ajt.14557

Hockenberry-Eaton, M. J. (Ed.). (1998). *Essentials of pediatric oncology nursing: A core curriculum*. Glenview, IL: Association of Pediatric Oncology Nurses.

Howell, R., Terry, S., Tait, V. F., Olney, R., Hinton, C. F., Grosse, S., & Glidewell, J. (2012). CDC grand rounds: Newborn screening and improved outcomes. *Morbidity & Mortality Weekly Report, 61*(21), 390–393. Retrieved from https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6121a2.htm

Ikuta, L. M. (2008). Human umbilical cord blood transplantation: What nurses need to know. *AACN Advanced Critical Care, 19*(3), 264–267. doi:10.4037/15597768-2008-3004

Intestinal Transplant Registry. (2005). The intestinal transplant registry. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/18670200

Jackson, R., & Roberts, E. (2001). Identification of neonatal liver failure and perinatal hemochromatosis in Canada. *Paediatrics and Child Health, 6*(5), 229–231. doi:10.1093/pch/6.5.248

Jara, P., Hierro, L., Martínez-Fernández, P., Alvarez-Doforno, R., Yánez, F., Diaz, M. C., . . . & López-Santamaría, M. (2009). Recurrence of bile salt export pump deficiency after liver transplantation. *New England Journal of Medicine*, *361*(14), 1359–1367.

Jones, S. A., & Karrer, F. M. (2014). Biliary atresia and choledochal cyst. In M. M. Ziegler, R. G. Azizkhan, D. von Allmen, & T. R. Weber (Eds.), *Operative pediatric surgery* (2nd ed., pp. 710–723). New York, NY: McGraw-Hill.

Kim, W. R., Lake, J. R., Smith, J. M., Schladt, D. P., Skeans, M. A., Harper, A. M., . . . Kasiske, B. L. (2018). OPTN/SRTR 2016 Annual data report: Liver. *American Journal of Transplantation, 18*(Suppl. 1), 172–253. doi:10.1111/ajt.14559

Kline, N. E. (Ed.). (2014). *Essentials of pediatric hematology/oncology nursing: A core curriculum* (4th ed.). Glenview, IL: Associate of Pediatric Oncology Nurses.

Lerret, S., & Stendahl, G. (2017). Pediatric solid organ transplantation. In S. Cupples, S. Lerret, V. McCalmont, & L. Ohler (Eds.), *Core curriculum for transplant nurses* (2nd ed., pp. 718–768). Philadelphia, PA: Wolters Kluwer.

Mangus, R. S., & Subbarao, G. C. (2013). Intestinal transplantation in infants with intestinal failure. *Clinics in Perinatology, 40*(1), 161–173. doi:10.1016/j.clp.2012.12.010

Oellerich, M., & Armstrong, V. W. (2001). The MEGX Test: A tool for the real-time assessment of hepatic function. *Therapeutic Drug Monitoring, 23*(2), 81–92. doi:10.1097/00007691-200104000-00001

Organ Procurement and Transplantation Network. (n.d.). Liver. Retrieved from https://optn.transplant.hrsa.gov/data/organ-datasource/liver

Organ Procurement and Transplantation Network. (2012). Retrieved from http://optn.transplant.hrsa.gov

Organ Procurement and Transplantation Network. (2016). *Policies*. Retrieved from https://optn.transplant.hrsa.gov/media/1217/06-2016_optn_abo_policies.pdf

Organ Procurement and Transplantation Network. (2018). Retrieved from https://optn.transplant.hrsa.gov

Organ Procurement and Transplantation Network. (2019a). *National data*. Retrieved from https://optn.transplant.hrsa.gov/data/view-data-reports/national-data

Organ Procurement and Transplantation Network. (2019b). Policies. Retrieved from https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf

Organ Procurement and Transplantation Network & Scientific Registry of Transplant Recipients. (2011). *OPTN/SRTR 2010 annual data report*. Rockville, MD: Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation.

Organ Procurement and Transplantation Network & Scientific Registry of Transplant Recipients. (2018). *OPTN/SRTR 2016 annual data report*. Rockville, MD: Department of Health and Human Services, Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation. Retrieved from https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/#

Pomposelli, J. J., & Burns, D. L. (2002). Nutrition support in the liver transplant patient. *Nutrition in Clinical Practice, 17*(6), 341–349. doi:10.1177/0115426502017006341

Reyes, J. (2014). Intestine transplantation. In M. M. Ziegler, R. G. Azizkhan, D. von Allmen, & T. R. Weber (Eds.), *Operative pediatric surgery* (2nd ed., pp. 1317–1326). New York, NY: McGraw-Hill.

Seattle Children's Hospital. (2015). Intensive Care Unit (ICU) Guideline of Care.10286 Heart Failure/Pre-Op Heart Transplant. © 2015 Seattle Children's All Rights Reserved.

Shearer, W. T., Lubin B. H., Cairo, M. S., Notarangelo, L. D., Hord, J., Crouch, G., . . . Wang, J. (2017). Cord blood banking for potential future transplantation. *Pediatrics, 140*(5), e20172695. doi:10.1542/peds.2017-2695

Smith, J. M., Weaver, T., Skeans, M. A., Horslen, S. P., Noreen, S. M., Snyder, J. J. . . . Kasiske, B. L. (2019, February 27). OPTN/SRTR 2017 Annual data report: Intestine. *American Journal of Transplantation, 19*, 282–322. doi:10.1111/ajt.15277

Tiao, G. M. (2014). Liver transplantation. In M. M. Ziegler, R. G. Azizkhan, D. von Allmen, & T. R. Weber (Eds.), *Operative pediatric surgery (*2nd ed., pp. 1306–1316). New York, NY: McGraw-Hill.

United Network for Organ Sharing. (2002). Critical pathway for the organ donor. Retrieved from https://www.unos.org/wp-content/uploads/unos/Critical_Pathway.pdf

U.S. Department of Health & Human Services. (2017). Scientific registry of transplant recipients (Annual data report). Retrieved from http://srtr.transplant.hrsa.gov/annual_reports/Default.aspx

Webber, S. A. (2014). Pediatric heart transplantation. In A. D. Kirk, S. J. Knechtle, C. P. Larsen, J. C. Madsen, T. C. Pearson, & S. A. Webber (Eds.), *Textbook of organ transplantation* (1st ed., Vol. 2, pp. 1406–1419). Chichester, England: John Wiley & Sons.

West, L. J. (2011). ABO-incompatible hearts for infant transplantation. *Current Opinion in Organ Transplantation, 16*, 548–554. doi:10.1097/MOT.0b013e32834a97a5

Zargar, S. A., Yattoo, G. N., Javid, G., Khan, B. A., Shah, A. H., Shah, N. A., . . . Shafi, H. M. (2004). Fifteen-year follow-up of endoscopic injection sclerotherapy in children with extrahepatic portal venous obstruction. *Journal of Gastroenterology and Hepatology, 19*(2), 139–145. doi:10.1111/j.1440-1746.2004.03224.x

CHAPTER 28

Extremely Low Birth Weight (ELBW) Infant

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INTRODUCTION

Recent advances in neonatal intensive care unit (NICU) technology and research in this area have improved the survival of extremely preterm infants. The extremely low birth weight (ELBW) infant, one who is born weighing less than 1,000 g, is a frequent resident of most modern NICUs. The survival rate for ELBW infants has improved (Doyle et al., 2011; Kilbride, 2004) as a result of advances in technology, organization of perinatal care (Rozé & Bréart, 2004), and obstetrical interventions (e.g., antenatal corticosteroid use; Kilbride, 2004). Survival rates to hospital discharge range from 26.5% to 87.8% (Guillen et al., 2011); the variations may be explained by strategies used to report rates (i.e., denominator bias) or differences in available resources, particularly in developing countries (Ballot, Chirwa, & Cooper, 2010). Greater survival, however, has not always been associated with increased quality-adjusted survival (Kilbride, 2004). The rate of survival of periviable infants (22–24 weeks' gestation) has improved from 30% to 36% between 2000 and 2011 in a large cohort from 11 centers affiliated with the National Institute of Child Health and Human Development (NICHD) network (Younge et al., 2017). We must strive for better neonatal outcomes of extremely premature infants and propose evidence-based strategies to improve the quality of perinatal, neonatal, and post discharge care with the goal to improve the long-term neurodevelopmental outcomes of ELBW infants (Rozé & Bréart, 2004). This chapter reviews the challenges facing an ELBW infant and its family.

EVIDENCE-BASED NEONATAL NURSING CARE

Over the past 45 years, it has become clear that preterm infants are a heterogeneous population who require very specialized treatment depending on their birth weight (Silverman, 1992). All preterm infants were viewed as "low birth weight or small infants," and their care usually reflected a variation on general pediatric care. The definition of low birth weight (LBW) now includes both ELBW and very low birth weight (VLBW); an infant who is born weighing less than 1,500 g. Whatever the reasons for the ELBW status, these neonates require highly specialized care if they are to survive and thrive. In the 1950s and 1960s, healthcare professionals realized that neonates, especially those who were sick and premature, required care based on an understanding of the pathophysiology of their diseases and identification of rigorously evaluated treatment (Silverman, 1992). Examples such as the development of retinopathy of prematurity (ROP) secondary to the use of unrestricted oxygen therapy and development of kernicterus from the use of sulfisoxazole underscore the importance of evidence-based practice (Silverman, 1992). Moving evidence to practice will be imperative to improving neonatal outcomes (Cumming, Hutchinson, Scott, Norton, & Estabrooks, 2010; Straus, Graham, & Mazmanian, 2006).

IMPACT OF BIRTH OF ELBW INFANTS

Decision Making in the Delivery Room

Appropriate for gestational age (AGA) infants less than 23 weeks' gestation and less than 500 g birth weight are considered too immature to survive based on data collected over the past 10 to 15 years (Seri & Evans, 2008). For example, the EPICure study undertaken in the United Kingdom found that less than 1% of infants born at 22 to 23 weeks' gestation survived and were discharged from the hospital (Costeloe, Hennessy, Gibson, Marlow, & Wilkinson, 2000). In contrast, most infants born greater than or at 25 weeks' gestation and greater than or at 600 g survive, and about half survive without severe long-term disabilities (Seri & Evans, 2008). A single study from Canada revealed that only 4% of infants born less than 500 g survived, all survived infants had short-term morbidities, and 27% of survived infants had no long-term neurodevelopmental impairments (Bashir et al., 2017). In another study from the United States, the survival rates of infants born at 22, 23, and 24 weeks' gestation were 31%, 42%, and 64%, respectively (Anderson et al., 2016). In Japan, the survival rates of infants with birth weight less than or equal to 300 g, 301 to 400 g, and 401 to 500 g were 18%, 41%, and 60%, respectively (Inoue et al., 2017). A review of studies showed a progressive increase in the rate of survival of infants born between 22 to 25 weeks' gestational age (American College of Obstetricians and Gynecologists [ACOG] & Society for Maternal–Fetal Medicine [SMFM], 2017; Ancel et al., 2015; Costeloe et al., 2012; Moore, Lemyre, Barrowman, & Daboval, 2013; Rysavy et al., 2015; Stoll et al., 2010). The survival and outcome of outborn infants are not similar to that of inborn infants. Outborn infants have been shown to have significantly higher risk of death or neurodevelopmental impairments, death alone, and cerebral palsy compared to inborn

preterm infants admitted to Canadian NICUs (Amer et al., 2018). ELBW infants, particularly those with birth weights between 500 and 599 g, have uncertainty and remained in the "gray zone" in terms of both survival and their long-term neurodevelopmental outcomes (Seri & Evans, 2008). As a result, issues related to moral status (Smith, 2005) and judgments about survival and unacceptable quality of life pose a dilemma for healthcare professionals, parents, and society (Powell et al., 2012; Seri & Evans, 2008).

An ELBW infant gains status as a patient and in a social sense as a member of a family once the infant is born. Healthcare professionals owe the ELBW infant a duty of ethical treatment and care because of this status (Smith, 2005). Whether to resuscitate and to initiate and continue intensive care raises questions related to the primacy of the newborn's best interest, respect for persons and legal rights, and the healthcare providers' consideration of ethical principles of beneficence, nonmaleficence, autonomy, justice, and futility. Ethical principles are difficult to implement in practice (Lorenz, 2003; Powell et al., 2012; Seri & Evans, 2008; Wilder, 2000). Treatment decisions for the ELBW infant reflect varied opinions on the proper approach to resuscitation and initiation of intensive care for these infants. The best interest of the child, which supports the universal right to life, is regulated by law in many countries (e.g., United States of America, United Kingdom, and Canada; Albersheim, 2008; Kopelman, 2005; Schoonakker & Smith, 2007) and is supported by the Hippocratic Oath and professional medical organizations (Haward, Kirshenbaum, & Campbell, 2011). Clinicians would therefore be inclined to initiate all necessary life support, at least temporarily, to permit assessment of the harm-to-benefit ratio based on projected suffering and burden as determined by current data or "best guess" (Smith, 2005). This approach includes an opportunity for survival while minimizing risk of long-term disability if the child is incorrectly judged to be nonviable and survives (Wilder, 2000).

The best interest standard is, however, difficult to apply for decision making in the delivery room, given the subjective nature of appraising the mortality and morbidity of infants in the "gray zone" or threshold of viability. Additionally, care providers must consider parents' or guardians' expectations, values, and religious beliefs, as they are the primary caregivers and will have the ultimate responsibility of care (Haward et al., 2011; Kopelman, 2005; Schoonakker & Smith, 2007). A "negative" analysis of the best interest of the child has been proposed, as it permits considerations of available options based on a range of moral, social, and legal issues. It also permits involvement of parents in decision making (Kopelman, 2005; Schoonakker & Smith, 2007). The American Academy of Pediatrics (AAP) promotes involvement of parents early in the decision-making process regarding survival and disability; hence, it incorporates parents' wishes to be involved in decision making (Schoonakker & Smith, 2007). A single approach or philosophy on care that is appropriate for all countries, cultures, or communities is an unreasonable expectation. Individual and societal values; long-term outcomes; associated physical, psychological, emotional, and financial costs; and finite resources will play a significant role in decision making regarding whether or not to resuscitate and continue care for ELBW infants. The marked variation in the frequency with which aggressive resuscitation is initiated in the zone of uncertainty is not surprising given the various ways in which competing values may be balanced by different individuals, cultures, and societies (Lorenz, 2003).

Ideally, a resuscitation plan should be in place prior to delivery. The most recent Neonatal Resuscitation Program (NRP) guidelines (7th edition), released by the AAP (Weiner & Zaichkin, 2016; Finan, Campbell, Aziz, & McNamara, 2017) recommend an individualized approach to management decisions regarding the aggressive resuscitation of ELBW infants. The other key changes in delivery room resuscitation include a focus on teamwork, communication, leadership skills, and predelivery briefing (Weiner & Zaichkin, 2016; Finan et al., 2017). Statistical modeling is being employed to identify factors (e.g., higher birth weight, female sex, singleton gestation, antenatal corticosteroids) that can assist clinicians in predicting morbidity and mortality and guide decision making (Powell et al., 2012; Tyson, Parikh, Langer, Green, & Higgins, 2008). In many instances though, there is often little time to make informed decisions about the reasonableness of resuscitation and initiation of intensive care (Powell et al., 2012). Contextual factors such as the woman's pain, labor, or deteriorating maternal or fetal condition, and inconsistent and conflicting information provided by multiple care providers pose a barrier to effective communication and decision making regarding resuscitation and delivery room care (Tomlinson, Kaempf, Ferguson, & Stewart, 2010). A standardized evidence-based approach to counseling that included recommendations for and against treatment was well received by patients, who found the process useful and consistent and the information understandable. More importantly, patients were comfortable with the decisions they made for themselves and their families (Tomlinson et al., 2010).

Ethical decisions regarding the extent of resuscitation efforts should be based on multiple factors including gestational age, birth weight, and fetal condition on antenatal ultrasound; the infant's condition at birth, survival, and morbidity data; and the parents' wishes. Information should be provided in a consistent manner, and a multidisciplinary approach will ensure that a range of concerns and areas of clinical care are addressed (ACOG & SMFM, 2017). The plan should be based on consensus decision making by parents and all healthcare professionals involved in the provision of care to the mother and ELBW infant (Powell et al., 2012; Wilder, 2000).

Survival of ELBW Infants

Data based on gestational age are more appropriate than data based on birth weight for projecting survival and future disability in infants. However, unreliable gestational age estimates, and earlier reporting practices of rounding off gestational age to the nearest week of gestation, can have a significant impact on survival statistics (Ho & Saigal, 2005). Population-based, international neonatal network studies examining survival between 24 and 29 weeks' gestational age of infants, weighing less than 1,500 g report marked variation in survival rates among different geographic areas (Helenius et al., 2017). These variations are likely a reflection of management styles such as proactive versus less aggressive resuscitation and initiation of intensive care, and manner in which outcomes are reported (e.g., duration of survival; Haward et al., 2011; Ho & Saigal, 2005; Lorenz, 2004). Table 28.1 illustrates the variation in survival rates of ELBW infants around the world by comparing countries such as the United States, Europe, Canada, and Japan. As is evident, with each additional week of gestational age, there is a large improvement in survival rates (Haward et al., 2011). At comparable gestational age and birth weight, mortality rates are higher for males compared to females (ACOG & SMFM, 2017).

Morbidity in ELBW Infants

Intraventricular hemorrhage (IVH), bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), ROP, and disabilities in mental and psychomotor development, neuromotor function, or sensory and communication function are major neonatal morbidities associated with ELBW (ACOG & SMFM, 2017; Ho & Saigal, 2005; Håkansson, Farooqi, Holmgren, Serenius, & Högberg, 2004).

Bronchopulmonary Dysplasia. BPD, the most prevalent multifactorial morbidity in ELBW infants, occurs in 10,000 to

TABLE 28.1

SURVIVAL RATES TO HOSPITAL DISCHARGE AMONG INFANTS BORN 22 TO 25 WEEKS GESTATION

Cohort	Year	Denominator	22 Weeks	23 Weeks	24 Weeks	25 Weeks
Japan: Single center (Iijima, Arai, Ozawa, Kawase, & Uga, 2009)	1991–2006	Live births	25%	47%	50%	–
EPICure (United Kingdom, Ireland; Wood, Marlow, Costeloe, Gibson, & Wilkinson, 2000)	1995	Population-based (LB + SB)	1%	11%	26%	44%
The EPIPAGE-2 study, France (Ancel et al., 2015)	1997–2011	Live births	0%	1.1%	31.2%	59%
EPIBel (Vanhaesebrouck et al., 2004)	1999–2000	Population-based	0%	6%	29%	56%
Norwegian Infant Study (Markestad et al., 2005)	1999–2000	Admission to NICU Population-based	0% 0%	39% 16%	60% 44%	80% 66%
Iowa, USA (Kyser, Morriss, Bell, Klein, & Dagle, 2012)	2000–2009	NICU admissions	33%	58%	87%	–
Switzerland (Fischer, Steurer, Adams, & Berger, 2009)	2000–2004	Population-based	0%	5%	30%	50%
Germany (Mehler et al., 2012)	2000–2007	Live births	41%	76%	82%	80%
Japan: Neonatal Research Network, Japan, (Ishii, Kono, Yonemoto, Kusuda, & Fujimura, 2013)	2003–2005	Live births	37%	64%	78%	86%
Japan: Multicenter (Kusuda et al., 2006)	2003	Live births	36%	78%	75%	–
NICHD (United States; Stoll et al., 2010)	2003–2007	Live births	6%	26%	55%	72%
EXPRESS (Sweden; Fellman et al., 2009)	2004–2007	Live births Population-based	12% 7%	54% 34%	71% 60%	82% 73%
California, USA (H. C. Lee et al., 2010)	2005–2008	Live births	5%	28%	60%	–
California, USA (Anderson et al., 2016)	2007–2011	Live births	6.4%	27%	60%	78%
NICHD (United States; Stoll et al., 2015)	2008–2012	Live births	32%	62%	77%	85%
Cochrane Database of Systematic Reviews (Lemyre, Davis, De Paoli, & Kirpalani, 2017)	2010–2015	Population-based	18%	41%	67%	79%

EPIBel, extremely preterm infants in Belgium; EPICure, extremely preterm infant cohort in the United Kingdom and the Republic of Ireland; EXPRESS, extremely preterm infants in Sweden study; LB, live birth; NICHD, National Institutes of Health Center for Child Health and Human Development; NICU, neonatal intensive care unit; SB stillbirth; VON, Vermont Oxford Network.

Note: Infants surviving greater than 12 hours.

Source: Reprinted from Haward, M. F., Kirshenbaum, N. W., & Campbell, D. E. (2011). Care at the edge of viability: Medical and ethical issues. *Clinics in Perinatology, 38*(3), 471–492. doi:10.1016/j.clp.2011.06.004. Copyright with permission from Elsevier.

15,000 infants annually in the United States (Jensen & Schmidt, 2014). The risk of BPD in ELBW infants is approximately 40% (Horbar et al., 2017). The rate of BPD varies from 57% to 70% in infants born at 23 weeks' gestational age. At 24 weeks' gestational age, rates of BPD range from 33% to 89%, and at 25 weeks' gestational age rates range from 16% to 71%. BPD is also associated with poor nutrition and growth, poor feeding skills, prolonged hospitalization, and episodes of nosocomial infection, and thus can have influences on later life and development. The "new BPD" (post surfactant disease, post acinar arrest during lung development) that occurs primarily in ELBW infants is thought to have a qualitatively different pathogenesis marked by immaturity and alveolar hypoplasia rather than the hyperoxic barotrauma or volutrauma typically seen in surfactant-deficient lungs (Narendran et al., 2003). Given the controversy and limitations of the current clinical definitions of BPD, two new definitions of BPD were proposed in the United States and Canada. These new definitions were noninvasive ventilation support and radiographic changes to objectively grade the severity of BPD (Higgins et al., 2018; Isayama et al., 2017). Based on these two new definitions (Higgins et al., 2018; Isayama et al., 2017), and gestational age, the prevalence of BPD and the risk of neurodevelopmental impairments will be different in infants with BPD and require further investigation.

The aim is to reduce the risk of BPD in ELBW infants by adopting a multipronged approach. Early delivery room or prophylactic surfactant prior to stabilization with continuous positive airway pressure (CPAP) regardless of respiratory status has demonstrated beneficial outcomes such as reduced delivery room intubations and days on mechanical ventilation, use of postnatal steroids, lowered oxygen saturation goals, fewer infants discharged home on oxygen, and decreased incidence and severity of BPD (Geary, Caskey, Fonseca, & Malloy, 2008; Meyer, Mildenhall, & Wong, 2004; Narendran et al., 2003). However, a recent systematic review concluded that there are no clear benefits of using prophylactic surfactant when infants are routinely managed on CPAP. With routine application of CPAP as standard of practice, the risk of BPD or death was lower with selective treatment with surfactant when compared with prophylactic use of surfactant (Rojas-Reyes, Morley, & Soll, 2012). Postnatal steroids, especially dexamethasone treatment, have been found to have no effect on BPD and are associated with gastrointestinal perforation and decreased growth in ELBW infants (Stark et al., 2001). More importantly, a systematic review reported a dramatic increase in neurodevelopmental impairment in preterm infants treated with glucocorticoids in the postnatal period (Barrington, 2001). A recent randomized controlled trial showed that extremely preterm infants who received a low dose of prophylactic hydrocortisone have a better rate of survival without BPD at 36 weeks post menstrual age (PMA; Baud et al., 2016). Also, those infants who received low-dose hydrocortisone and were born at 24 and 25 weeks' gestation had better neurodevelopmental outcomes (Baud et al., 2019). Chronic oxygen dependency in BPD infants who were discharged home with oxygen does not increase the extra risk of neurodevelopmental impairments compared to infants with BPD alone (Lodha et al., 2014).

Poets et al. have suggested some possible strategies to prevent the risk of BPD, including nasal CPAP in place of intubation and mechanical ventilation, exogenous surfactant via minimally invasive administration technique with a thin tracheal catheter/nasogastric tube, volume targeted ventilation if mechanical ventilation is necessary, synchronized intermittent positive pressure ventilation (iPPV), early use of caffeine, vitamin A, consideration of low-dose hydrocortisone for the first 10 postnatal days, and consideration of intravenous dexamethasone in infants who required mechanical ventilation at the end of their second postnatal week (Poets & Lorenz, 2018).

Necrotizing Enterocolitis. NEC, an acquired gastrointestinal disease that complicates the neonatal course of survivors, affects 1 to 3 infants per 1,000 live births (Guthrie et al., 2003; J. S. Lee & Polin, 2003). ELBW infants are particularly susceptible and have a higher incidence of NEC; however, the clinical presentation is relatively similar to that for other affected neonates. The cause of NEC remains unclear but most likely represents a complex interaction of factors with a final common pathway of intestinal ischemia. In epidemiologic studies, prematurity is consistently identified as an independent determinant of NEC (J. S. Lee & Polin, 2003). Other factors include feeding practices, intestinal ischemia, and bacterial colonization (Kliegman, 1990). The risk of NEC associated with blood transfusion is increasing, but the causality of the blood transfusion itself or the underlying anemia remains unresolved. Currently, we believe that transfusion/anemia-associated NEC is a possible biological plausibility (Maheshwari, Patel, & Christensen, 2018).

Manifestations of NEC include abdominal distention, increased gastric residuals, vomiting and/or bilious aspirates, bloody stools, metabolic acidosis, cellular destruction, and gut necrosis. Hallmarks of NEC include pneumatosis intestinalis, hepatic portal venous gas, perforation, and pneumoperitoneum; these are evident on abdominal radiograph (Meerstadt & Gyll, 1994; Walsh & Kliegman, 1986). Treatment focuses on medical stabilization and interventions including bowel rest, gastric decompression, broad-spectrum systemic antibiotics, and parenteral nutrition. Infants with perforation either are operated on or have a peritoneal drainage (J. S. Lee & Polin, 2003). The catastrophic nature of NEC and the fragility of ELBW infants are evident in the overall mortality of the disease, which is approximately 50% (Blakely et al., 2005). Once NEC develops, the long-term consequences may include growth delay and severe neurodevelopmental impairments (Dilli, Eras, Özkan Ulu, Dilmen, & Durgut şakrucu, 2012; Salhab, Perlman, Silver, & Sue Broyles, 2004; Soraisham, Amin, Al-Hindi, Singhal, & Sauve, 2006). Infants with NEC requiring surgical treatment are associated with significantly lower mental developmental index (MDI) and psychomotor development index (PDI) scores (Allendorf et al., 2018). Consequently, prevention of NEC has been the primary focus, resulting in numerous approaches being proposed to prevent NEC (Neu & Walker, 2011).

Provision of small volumes of exclusive human milk (Meinzen-Derr et al., 2009) or human milk fortified with a human milk–derived fortifier (Sullivan et al., 2010) has been found to be safe (i.e., lower incidence of NEC). Standardized feeding regimens have been introduced in an attempt to reduce the incidence of NEC by minimizing variations in enteral feeding practices. A systematic review and meta-analysis of observational studies ("before" and "after") reported a reduced incidence of NEC after the introduction of a standardized feeding regimen (Patole & de Klerk, 2005). A retrospective cohort study reported an association between prolonged duration of initial (i.e., in the first 3 postnatal days) antibiotic course and increased risk of NEC or death (Cotten et al., 2009). Based on a recent systematic review of randomized controlled trials, it has become evident that the use of prophylactic probiotics reduced the risk of NEC (stage 2 and greater) by 44% and also reduced the risk of mortality (Deshpande, Jape, Rao, & Patole, 2017). Therefore, most NICUs are using probiotics as a standard of care in their units; however, controversy remains with regard to the type of probiotic that should be used to reduce the risk of NEC. In another study from Germany, Denkel et al. (2017) recommend the routine use of dual-strain probiotics in standard neonatal care of infants born less than 1,000 g for prevention of NEC. Use of oral immunoglobulin (Foster, Seth, & Cole, 2017) as a preventative strategy for NEC is not supported in preterm or LBW

infants; however, the strategy has not been studied exclusively in ELBW infants. Supplementation of *L*-arginine in extreme preterm infants may also be protective in prevention of NEC (Mitchell et al., 2014). The roles of pentoxifylline and/or lactoferrin in prevention of NEC are not yet well studied in a large randomized controlled trial, and therefore evidence is still lacking for use of either agent as the standard of care in modern NICUs (Pammi & Haque, 2015; Pammi & Suresh, 2017).

Retinopathy of Prematurity. ROP, a vascular proliferative disorder of the immature retina (i.e., abnormal growth of retinal capillaries during vascularization), causes acuity defects, refractive errors (particularly myopia), gaze abnormalities, and blindness (Andersen & Phelps, 2000). Vascularization of the retina is complete by 40 weeks' gestational age (Brion, Bell, & Raghuveer, 2003). The developing retinal capillaries are susceptible to injury; hence, preventative strategies (e.g., control of exogenous oxygen delivery) are aimed at reducing stress contributing to injury, while other treatment approaches (e.g., cryosurgery or laser ablation) are aimed at controlling or arresting progression of neovascularization (Phelps & Watts, 2001).

The prevalence of ROP (any stage) in infants born less than 27 weeks' gestational age was reported at 73% and the prevalence of severe ROP was reported at 35% (Austeng, Källen, Ewald, Jakobsson, & Holmström, 2009). In developed countries, the population at risk for blinding ROP has changed, with studies (Hardy et al., 2004) suggesting that ELBW infants are at greatest risk of advanced stages of ROP requiring treatment (Gilbert et al., 2005). In contrast, in low- and moderate-income countries, it is the larger, more mature infants that are at risk of developing severe ROP (Gilbert et al., 2005). To facilitate earlier identification and timely intervention for prethreshold ROP in at-risk infants (i.e., ELBW), it is recommended that the timing of an eye examination be based on chronologic age of 4 to 6 weeks rather than 31- to 33-week postconceptional age being used (Subhani, Combs, Weber, Gerontis, & DeCristofaro, 2001). Fierson et al., (2013) recommend the use of the international classification system (2005) to grade severity of ROP based on retinal examinations. Subsequent eye examinations, depending on the results, occur at least every 1 to 2 weeks until the retina is fully vascularized. Continued ophthalmologic follow-up of ELBW infants with severe ROP is essential as ROP may represent a lifelong disease, as evidenced by the number of eyes, both cryotherapy-treated and noncryotherapy-treated, that developed retinal detachment, blindness, and other related complications between ages 10 and 15 years (Palmer et al., 2005).

In premature infants, factors such as change in oxygen exposure have been proposed to cause distribution in the vascularization. In a systematic review, supplementation with vitamin E, an antioxidant agent, was not supported, given that there was an increased risk of sepsis and reduced risk of severe retinopathy and blindness among VLBW infants who were given vitamin E supplements (Brion et al., 2003). Darlow and Graham (2011) found that with vitamin A supplementation fewer infants required oxygen at 36 weeks' PMA (numbers needed to treat 13, 95% CI 7, 100). Supplementation with vitamin A, the precursors of which have antioxidant properties, has been shown in a systematic review to be a potential protective therapy for ROP in ELBW infants as there was a trend toward reduced incidence of ROP in treated infants. Askie, Henderson-Smart, and Ko (2009) performed a systematic review of studies of unrestricted oxygen use and outcomes in premature infants. They found that if oxygen levels were not monitored closely, morbidity in this population rose. Oxygen levels, therefore, must be watched and controlled carefully; however, the optimal range of oxygen levels remains unknown (Askie et al., 2009). Hyperoxia may produce vascular endothelial growth factor (VEGF) in the process of development of severe ROP. Intravitreal bevacizumab/ranibizumab, an anti-VEGF agent, is being used as a newer monotherapy for severe ROP and reduces the risk of refractive errors during childhood. It does not reduce the risk of retinal detachment or recurrence of ROP in infants with severe ROP (Sankar, Sankar, & Chandra, 2018).

Cryotherapy and laser therapy are standard care for threshold ROP (Palmer et al., 2005). Given the substantial proportion of eyes treated with cryotherapy that developed retinal detachment and unfavorable distance visual acuity, current research is focusing on early treatment for ROP (Hardy et al., 2004; Subhani et al., 2001). A systematic review by Andersen and Phelps (2009) has reported early treatment with peripheral retinal ablation to be effective for treating eyes determined to be at high risk for a poor outcome or prethreshold ROP. Treatment resulted in reduced risk of adverse structural outcome at 12 months and 5½ years with corresponding reduction in adverse acuity. When laser therapy has been used in conjunction with bevacizumab/ranibizumab, it has been shown to reduce the risk of retinal detachment and recurrence of ROP in infants with type 1 ROP. However, this treatment needs a large randomized controlled trial to determine the efficacy of intravitreal bevacizumab/ranibizumab in combination with laser treatment in severe ROP (Sankar et al., 2018).

Neurodevelopment. Major neurologic impairments include cerebral palsy, motor impairment, visual and hearing impairments, and cognitive deficits (Ho & Saigal, 2005; Wood et al., 2000). A recent systematic review of nine high quality studies reported severe neurodevelopmental delay in preterm infants born at 22, 23, 24, and 25 weeks' gestational age were 31%, 17%, 21%, and 14%, respectively, whereas rates of moderate-to-severe neurodevelopmental delay were 43%, 40%, 28%, and 24%, respectively (Moore et al., 2013). Significant variation in neurodevelopmental outcomes is reported in various cohorts of extremely preterm children (Haward et al., 2011). Variability in morbidity reported in various cohorts of extremely preterm children (Haward et al., 2011) is striking (Lorenz, 2003) and may be due to chronologic age at evaluation, varying criteria for defining and reporting neurologic impairments (i.e., instruments to measure disability and functional capacity; Haward et al., 2011; Ho & Saigal, 2005), differences in center demographics, antenatal interventions, and neonatal clinical practice or interventions (Vohr et al., 2004).

A study of 219 ELBW infant survivors admitted between 1992 and 1995 to Rainbow Babies and Children's Hospital in Cleveland, Ohio, and assessed at 8 years of age reported the following outcomes: (1) major neurosensory impairment, including cerebral palsy, deafness, and blindness (16%); (2) asthma requiring therapy (21%); (3) functional limitations including delay in growth or development, mental or emotional delay, need to reduce or inability to participate in physical activities, difficulty seeing, hearing, speaking, or communicating, and inability to play or socialize with others (64%); (4) one or more compensatory dependence needs, including prescribed medication, life-threatening allergic reactions, prescribed special diet, special equipment to see, hear, or communicate, and need for help or special equipment for walking, feeding, dressing, washing, and toileting (48%); and (5) services needed above routine, including visiting a physician regularly for a chronic condition, nursing care or medical procedures, occupational or physical therapy, special school arrangements, or an individualized education program (65%). The findings of this study may not be representative of all ELBW survivors, as this was not a population-based study. A recent population-based study of ELBW infants found up to 50% prevalence of neurodevelopmental

disability that remained throughout childhood (Johnson et al., 2009).

The ELBW infant follow-up group of the Vermont Oxford Network (VON) examined data from 33 North American VON centers for 1998, noting severe disability in 34% of infants (n = 3,567) assessed at 18 to 24 months' corrected age (CA; Mercier et al., 2010). Despite improvements in perinatal interventions, extremely preterm infants are still at an increased risk for adverse outcomes at 18 to 22 months CA (Hintz, Kendrick, et al., 2011). Neurodevelopmental outcomes for infants born at less than 25 weeks' estimated gestation age remained unchanged in infants born between 1991 and 2001 versus those born between 2002 and 2004: moderate-to-severe cerebral palsy (adjusted odds ratio [aOR] 1.52, 95 confidence interval [CI] 0.86, 2.71); p = .15), mental developmental index less than 70 (aOR 1.3, 95% CI 0.91, 1.87; p = .15), and neurodevelopmental impairment diagnosed in 50% of surviving infants (aOR 1.4, 95% CI 0.98, 2.04; p = .07; Hintz, Kendrick, et al., 2011). Neurodevelopmental and cognitive impairments have been found to remain stable between 6 and 11 years of age, with minimal shifts in severity of disability (Johnson et al., 2009). The proportion of ELBW survivors with adverse outcomes increases with decreasing gestational age (Haward et al., 2011), with poor chances of intact outcomes for infants at 23 and 24 weeks' gestation. At comparable gestational age and birth weight, disability rates (e.g., cerebral palsy) are higher for males than for females (ACOG & SMFM, 2017; Johnson et al., 2009). Gestational age and gender have independent effects on neurodevelopmental outcomes (Haward et al., 2011). In a recent study including 11 centers affiliated with the NICHD Neonatal Research Network in the United States, the survival of extreme premature infants between 22 to 24 weeks' gestation with neurodevelopmental impairments with or without neurosensory impairments is shown in Table 28.2 (Younge et al., 2017).

Severe brain injury as evidenced by abnormal cerebral ultrasound findings predicts major morbidity such as quadriparesis and severe cerebral palsy in ELBW infants (Kuban et al., 2009). Interventions such as prophylactic indomethacin therapy have been used in clinical practice to reduce the occurrence of severe IVH or periventricular leukomalacia, which are significant short-term predictors of neurodevelopmental morbidity in ELBW infants. Although prophylactic administration of indomethacin reduces the incidence of severe IVH (Schmidt et al., 2007), it does not improve neurodevelopmental outcomes (Fowlie, Davis, & McGuire, 2010; Schmidt et al., 2001). Magnesium sulfate given to mothers at risk of preterm birth has been shown to have neuroprotective effects, improving long-term outcomes of infants born preterm (Doyle, 2012); however, the most effective regimen remains to be determined (Bain, Middleton, & Crowther, 2012). The Caffeine for Apnea of Prematurity (CAP) trial, which enrolled infants less than 1,250 g, initially reported reduced rates of cerebral palsy and cognitive delay at 18 months of age; however, rates of disability were no different at 5 years CA (Schmidt et al., 2012).

Among other contributing factors, neurodevelopmental morbidity has been partially attributed to the stressful nature of the intensive care unit (Gorski, 1991). Neurodevelopment can be promoted if the potential impact of the environment is recognized and interventions including one or more elements such as control of external stimuli (e.g., light, noise, minimal stimulation), clustering of care activities, and positioning or swaddling are implemented (Venkataraman, Kamaludeen, Amin, & Lodha, 2018). There is evidence that this broad category of interventions, referred to as developmental care, offers the following benefits to preterm infants: improved short-term growth and feeding outcomes, decreased respiratory support needs, decreased length and cost of hospital stay, and improved neurodevelopmental outcomes to 24 months CA (Symington & Pinelli, 2006).

TABLE 28.2

NEURODEVELOPMENTAL OUTCOMES AT 18 TO 22 MONTHS OF CORRECTED AGE

Outcomes	Epoch 1 (2002–2003) No./Total No. (%)	Epoch 2 (2004–2007) No./Total No. (%)	Epoch 3 (2008–2011) No./Total No. (%)
All infants—survival with NDI	207/1,391 (14.9)	209/1,535 (13.6)	211/1,348 (15.6)
All infants—survival with NSI	73/1,380 (5.3)	66/1,533 (4.3)	92/1,348 (6.8)
Infants born at 22 weeks—survival with NDI	4/241(1.6)	9/274 (3.3)	5/234 (2.1)
Infants born at 23 weeks—survival with NDI	63/496 (12.7)	41/489 (8.4)	51/450 (11.3)
Infants born at 24 weeks—survival with NDI	140/654 (21.4)	159/772 (20.6)	155/664 (23.3)

NDI, neurodevelopmental impairment; NSI, neurosensory impairments.

Source: From Younge, N., Goldstein, R. F., Bann, C. M., Hintz, S. R., Patel, R. M., Smith, P. B., . . . Cotten, C. M. (2017). Survival and neurodevelopmental outcomes among periviable infants. *New England Journal of Medicine, 376*(7), 617–628. doi:10.1056/NEJMoa1605566

COMPLICATIONS OF BEING ELBW

In the immediate neonatal period, ELBW infants are more susceptible to all the possible complications of premature birth because of their very vulnerable state of development. The balance of this chapter is an overview of typical problems experienced by ELBW infants and some of the outcomes for these infants. The chapter also addresses the key areas for care where nurses can contribute to the scientific basis for practice.

Thermoregulation

Cold stress is associated with increased mortality and morbidity (e.g., hypoglycemia, respiratory distress, and metabolic acidosis) in premature infants (Hazan, Maag, & Chessex, 1991; McCall, Alderdice, Halliday, Jenkins, & Vohra, 2010). Quality improvement data for infants less than 750 g indicate that the incidence of temperature less than 36.5°C or 97.6°F varies between NICUs (Bhatt et al., 2007). In the first 12 hours of life, ELBW infants are not able to conserve heat, given poor vasomotor control (Knobel, Holditch-Davis, Schwartz, & Wimmer, 2009). A high body surface area-to-body weight ratio (Lyon, Pikaar, Badger, & McIntosh, 1997), and decreased ability to produce heat because of decreased brown fat stores and decreased glycogen supply, makes ELBW infants particularly vulnerable to hypothermia (defined as <36.5°C) (Knobel, Wimmer, & Holbert, 2005; McCall et al., 2010; Sauer, Dane, & Visser, 1984). Provision of warmth is the first step in the resuscitation of the newborn because the risk of cold

stress is greatest at birth (Knobel et al., 2005). Hence, clinicians should maintain the delivery room temperature at 23°C to 25°C (Weiner & Zaichkin, 2016). A systematic review (McCall et al., 2010) found that early intervention in the delivery room, particularly the application of plastic wraps (for infants <28 weeks' gestational age) or transwarmer mattresses (infants <1,500 g) immediately after birth, prevents hypothermia, keeping infants warmer on admission to the NICU. These early interventions are in addition to "routine" care implemented immediately after birth such as drying the infant thoroughly, especially the head, removing any wet blankets, wrapping the infant in a prewarmed blanket, covering the infant's head with a cap, keeping the temperature of the ventilator at greater than or equal to 34.0°C to 35.0°C, utilizing heated humidified gases, and prewarming any contact surfaces. Further research is required to facilitate firm recommendations of these early interventions in clinical practice for ELBW.

The "gold standard" for nursing preterm infants in incubators or under radiant warmers is to maintain the body temperature at which the metabolic rate reaches the minimum or thermoneutral temperature (Rieger-Fackeldey, Schaller-Bals, & Schulze, 2003). In the first week of life, this thermoneutral temperature depends on gestational age and postnatal age, after which time it depends on body weight and postnatal age (Sauer et al., 1984). However, for ELBW infants, this optimal body temperature is not known (Rieger-Fackeldey et al., 2003).

Respiratory Distress Syndrome

Respiratory distress syndrome (RDS), a common problem among ELBW infants, has a pathogenesis dominated by surfactant deficiency complicated by an overly compliant chest wall. Surfactant deficiency leads to decreased lung compliance, reduced alveolar ventilation, atelectasis, and alveolar hypoperfusion, which clinically manifests as grunting respirations, retractions, nasal flaring, cyanosis, and increased oxygen requirement shortly after birth. The findings of RDS on chest radiograph include low lung volume, reticulogranular pattern, ground glass appearance, air bronchograms, and difficult delineation of cardiac and lung borders (Hellmann, Millman, & Lodha, 2005). Clinical management includes prevention of RDS, surfactant replacement, and respiratory support. The prevention strategies include antenatal corticosteroids (Crowther, McKinlay, Middleton, & Harding, 2015; Roberts, Brown, Medley, & Dalziel, 2017). The mainstay of medical management is administration of surfactant in addition to supplemental oxygen, CPAP, humidified high-flow nasal cannula system, and/or ventilatory support, and the clinical course may be complicated by air leaks, significant shunting through the patent ductus arteriosus (PDA), or BPD (Hamvas, 2011; Rojas-Reyes et al., 2012).

Prophylactic (delivery room) and rescue (after established RDS) administration of surfactant reduces mortality associated with RDS in preterm infants (Rojas-Reyes et al., 2012). Prophylactic administration of surfactant has been reported to decrease the incidence of pneumothorax, the risk of pulmonary interstitial emphysema, and the risk of BPD (Rojas-Reyes et al., 2012). However, these differences were no longer evident when comparing infants routinely being managed on CPAP who received prophylactic versus rescue surfactant treatment. In fact, the risk of BPD or death was lower in the latter (Rojas-Reyes et al., 2012). Prophylactic administration of synthetic surfactant when compared to animal-derived surfactant has been noted to show a trend toward decreased mortality in the neonatal period and at 36 weeks PMA. No significant differences in risk of BPD were found between groups (Pfister, Soll, & Wiswell, 2009).

Endotracheal suctioning for mechanically ventilated patients in the NICU is customary nursing practice aimed at reducing buildup of secretions and tube obstruction, which can cause discomfort, hypoxemia, hypercapnia, and lobar collapse. Closed suctioning, that is, suctioning without disconnecting intubated ventilated neonates, may have certain short-term benefits: for example, reduction in episodes of hypoxia (typical relative risk 0.48, 95% CI 0.31, 0.74), smaller percentage change in heart rate (weighted mean difference 6.77, 95% CI 4.01, 9.52), and fewer number of infants experiencing bradycardia (typical relative risk 0.38, 95% CI 0.15, 0.92; Taylor, Hawley, Flenady, & Woodgate, 2011). Noninvasive ventilation including CPAP, synchronized iPPV, and nasal bilevel-CPAP significantly changed the management of RDS in the modern era of NICUs to prevent mechanical trauma due to ventilation pressure and volume (Salvo et al., 2017). Several other strategies for the management of RDS are under experiment, such as the use of noninvasive respiratory support with minimally or less invasive surfactant therapy (Kribs & Hummler, 2016). The less invasive surfactant administration (LISA) technique for surfactant delivery reduces the duration of mechanical ventilation and the composite outcome of death and/or BPD and BPD alone at 36 weeks' PMA in infants with RDS (Aldana-Aguirre, Pinto, Featherstone, & Kumar, 2017).

Hyperbilirubinemia

Among ELBW infants, differences in neurodevelopmental outcomes have been attributed to differences in maximum levels of serum bilirubin levels and duration of phototherapy (Mazeiras et al., 2012). High levels of unconjugated bilirubin are associated with kernicterus, a form of brain damage with sequelae such as deafness, mental retardation, and cerebral palsy. In ELBW infants, kernicterus can occur at low levels of serum bilirubin (Moll, Goelz, Naegele, Wilke, & Poets, 2011), and many clinicians have been inclined to initiate phototherapy at low serum bilirubin levels (<7–10 mg/dL; i.e., aggressive phototherapy; Ambalavanan & Whyte, 2003). These studies, however, may be biased toward overestimating bilirubin toxicity because most problems that cause developmental delay are also associated with hyperbilirubinemia (Ambalavanan & Whyte, 2003). A randomized controlled trial examining the benefits or harms of aggressive phototherapy versus conservative phototherapy at 18 to 22 CA months found no significant difference in the rate of death or neurodevelopmental impairment. However, subgroup analysis showed reduced death or neurodevelopmental impairment, and a significant reduction in the rates of hearing loss and profound neurodevelopmental impairment without an increase in the rate of death or other adverse outcomes (e.g., cerebral palsy, MDI score). Although aggressive phototherapy reduced neurodevelopmental impairment in infants weighing 501 to 750 g at birth, the rate of death was higher, thereby counterpoising the benefits of aggressive phototherapy treatment (Morris et al., 2008). When comparing risk-adjusted outcomes between ELBW infants who received phototherapy with those who did not receive phototherapy, phototherapy was not independently associated with death or neurodevelopmental impairment (Hintz, Stevenson, et al., 2011). However, the rate of profound delay as measured by Bayley Scales Mental Developmental Index less than 50 was higher in infants 501 to 750 g birth weight who did not receive phototherapy (Hintz, Stevenson, et al., 2011).

In VLBW infants, phototherapy may increase insensible water loss (Bell, Neidich, Cashore, & Oh, 1979) secondary to heat generated by the phototherapy equipment (Kjartansson, Hammarlund, & Sedin, 1992), thereby complicating fluid management. Other known harmful effects of phototherapy include an increase in the incidence of PDA (Rosenfeld et al., 1986), as well as a potential increase in the incidence of ROP (Yeo, Perlman, Hao, & Mullaney, 1998). The benefits and known and unknown adverse effects of phototherapy need to be weighed in decision making regarding initiation of phototherapy at low serum bilirubin levels (Ambalavanan &

Whyte, 2003). Nurses' vigilance in monitoring input and output and signs and symptoms of PDA can guide medical decision making regarding risks and benefits of phototherapy, as well as identify adverse consequences of phototherapy in the event treatment is initiated. Mild unconjugated hyperbilirubinemia may be physiologic in nature and it could be attributable to breastfeeding or breast milk jaundice, but it is essential to exclude significant pathologic conditions. Conjugated hyperbilirubinemia is always pathologic in nature and needs extensive laboratory workup (Feldman & Sokol, 2013; Martin, Fanaroff, & Walsh, 2015).

Apnea of Prematurity

Apnea is generally defined as periodic pauses in respirations lasting greater than 20 seconds, or shorter pauses associated with cyanosis, pallor, hypotonia, or bradycardia. However, varied definitions are also found with the proposed duration of pause being shorter (e.g., 15 seconds; Spitzer, 2012). A proposed pathophysiologic mechanism thought to contribute to AOP involves immaturity of reflex pathways initiated by hypercapnia, hypoxia, and upper airway afferents (Martin, Abu-Shaweesh, & Baird, 2004). Nevertheless, there are multiple secondary etiologic factors such as birth trauma, meningitis, seizures, cardiac causes (cyanotic congenital heart disease, hypertension or hypotension, PDA, increased vagal tone), infection, gastroesophageal reflux (GER), NEC, anemia or hypoxemia, metabolic disorder, drug therapy, and temperature instability that may contribute to apnea. AOP is a diagnosis of exclusion in infants less than 37 weeks' gestational age (Martin et al., 2004; Stokowski, 2005). There is uncertainty about the long-term consequence of recurrent AOP; however, concern relates to the impact of multiple prolonged episodes of hypoxemia and reflex bradycardia on organ systems such as the brain leading to brain injury and poor neurodevelopmental outcome (Henderson-Smart & De Paoli, 2010; Janvier et al., 2004). Extremely preterm infants who had prolonged hypoxemic episodes during the first 2 to 3 months after birth and survived to 36 weeks' PMA had adverse outcomes at 18 months CA (Poets et al., 2015).

The incidence of AOP increases as gestational age decreases. In ELBW infants, apneic and bradycardic episodes persist beyond term gestation, most likely secondary to the higher incidence of BPD. These persistent apneic and bradycardic episodes complicate and contribute to variability in management decisions related to discharge planning and may prolong hospital stays (Eichenwald, Aina, & Stark, 1997). Clinical interventions for AOP include tactile stimulation, oscillating mattress (kinesthetic stimulation), provision of thermoneutral environment, methylxanthine therapy, flow through nasal cannula, CPAP or ventilatory support, nasal CPAP or noninvasive positive pressure ventilation (NIPPV), and olfactory stimulation (Al-Alaiyan, Dawoud, & Al-Hazzani, 2014; Lemyre et al., 2017; Marlier, Gaugler, & Messer, 2005; Martin et al., 2004; Osborn & Henderson-Smart, 2000; Stokowski, 2005). Although some of these interventions such as methylxanthines (Henderson-Smart & De Paoli, 2010), doxapram (Henderson-Smart & Steer, 2004), and NIPPV (Lemyre et al., 2017) have been shown in a systematic review to be effective in reducing the number of apneic and bradycardic episodes in preterm infants, more research is required before these interventions can be recommended as standard therapy in ELBW infants specifically. The common side effects of doxapram include an increase in blood pressure, abdominal distension, jitteriness, irritability, increased gastric residuals, emesis, and seizures. There is insufficient evidence at this time to support the use of doxapram in regular practice.

Although current practice standards require nurses to document apnea/bradycardia episodes in order to facilitate management decisions, these records underestimate the frequency of events when compared to recordings (Razi, Humphreys, Pandit, & Stahl, 1999). Nurses spend a significant amount of time monitoring, assessing, and managing apneic and bradycardic episodes, given that nearly all ELBW infants experience AOP. There is a need to develop evidence-based criteria for a minimal safe observation period between the time of last apneic episode and hospital discharge (Eichenwald et al., 1997). It is commonly recommended to stop caffeine at 34 weeks' PMA and monitor for apneas at least 7 days before newborn discharge home at 36 weeks and beyond. Furthermore, a clear understanding of the impact of use of technology (e.g., home monitoring) on hospital discharge, subsequent rehospitalization, post discharge morbidities (Eichenwald et al., 1997), and family functioning and coping is required.

Patent Ductus Arteriosus

Premature infants, particularly ELBW infants, have a significant incidence of persistent PDA, a vascular connection between the aorta and pulmonary artery (Dollberg, Lusky, & Reichman, 2005). Reliable diagnosis of PDA in the first 4 days of life depends on echocardiography because of poor specificity of clinical signs (e.g., murmur, wide pulse pressure, bounding pulses, and increased precordial activity; Skelton, Evans, & Smythe, 1994). A cardiac murmur is more reliable after this time (Skelton et al., 1994). Metabolomics entails the measure of low molecular weight metabolites to determine the phenotype of a cell, tissue, or organism. Preliminary findings suggest that "the metabolomics analysis of the first urine passed by preterm infants can predict the persistent patency of the ductus arteriosus at 3 to 4 days of life, as demonstrated by echocardiography performed by an expert cardiologist" (Fanos, Antonucci, Barberini, Noto, & Atzori, 2012). Consequently, metabolomics may facilitate diagnosis of PDA (Fanos et al., 2012).

In a small proportion of ELBW infants, the PDA may close spontaneously or persist without clinical consequences. Studies show that premature infants born less than 30 weeks' gestational age have a spontaneous closure of the PDA greater than 50% of the time (Herrman, Bose, Lewis, & Laughon, 2009; Schmidt et al., 2001; Van Overmeire et al., 2004). Nevertheless, approximately 55% of ELBW infants require pharmacologic treatment as they are symptomatic (e.g., evidence of left to right shunting, difficulty weaning mechanical ventilation, or increased mechanical support because of worsening pulmonary status; Koch et al., 2006; Richards, Johnson, Fox, & Campbell, 2009). Treatment decisions for a diagnosed PDA are based on the clinical significance or clinical effect, the criteria for which vary among neonatologists (Wyllie, 2003). Infants with persistent PDA experience increases in mortality and morbidities such as more prolonged and severe RDS, BPD, and NEC (Dollberg et al., 2005) that may be attributed to their prematurity or PDA (Koch et al., 2006). The use of pharmacologic intervention and surgical ligation has recently decreased in VLBW infants with PDA (Ngo, Profit, Gould, & Lee, 2017).

Prophylactic treatment circumvents the challenges of deciding whether or not a PDA is significant (Wyllie, 2003). Prophylactic administration of indomethacin, a nonselective cyclooxygenase, reduces the incidence of symptomatic PDA and the need for surgical duct ligation. Adverse effects of indomethacin, including NEC, excessive bleeding, or sepsis, were no different between preterm infants receiving prophylactic indomethacin and controls. The incidence of oliguria was increased; however, this was not associated with major renal impairment. Although prophylactic administration of indomethacin reduces the incidence of severe IVH, it did not improve neurodevelopmental outcomes (Fowlie et al., 2010; Schmidt et al., 2001). Furthermore, approximately 64% of preterm infants are medicated unnecessarily (Wyllie, 2003). Values attached by healthcare providers and parents to the benefits and

risks of prophylactic treatment with indomethacin will guide the implementation of this intervention (Fowlie et al., 2010). According to Fanos, Pusceddu, Dessì, and Marcialis (2011), indomethacin prophylaxis should be abandoned as it "unethically exposes newborns who will never have a persistent PDA to the side effects of drugs" and "cannot be recommended for the prevention of long-term morbidities and mortality, especially in centers where severe IVH is comparable to the national average and surgical complications are minimal." Similarly, ibuprofen, also a cyclooxygenase inhibitor, unnecessarily compromises the infant's renal and gastrointestinal systems without conferring benefits in those ELBW infants with spontaneous closure of PDA. Consequently, prophylactic ibuprofen is not recommended (Fanos et al., 2011; Ohlsson & Shah, 2011). Advantages of prophylactic surgical closure of PDA include reduced incidence of stage II and III NEC; however, no reductions were noted in mortality or BPD. Again, given the rate of spontaneous closure of PDA in ELBW infants and potential risks associated with surgery, prophylactic surgical closure is not recommended (Fanos et al., 2011; Ohlsson & Shah, 2011).

Both ibuprofen and indomethacin are effective in closing a PDA diagnosed either clinically or by echocardiogram at less than 28 days. No statistically significant difference was noted in failure of ductal closure, all causes of mortality, neonatal mortality, infant mortality, and common neonatal morbidities (e.g., BPD, IVH, ROP, and infection). Ibuprofen was deemed superior based on biochemical and physiologic data suggesting that it has less adverse effects on organs (e.g., kidneys, gastrointestinal system, and brain; Ohlsson, Walia, & Shah, 2010). Other interventions include fluid restriction and use of diuretics; however, there is little evidence to support their routine use in clinical practice (Wyllie, 2003). Furosemide, which increases prostaglandin production, is often given in conjunction with indomethacin to prevent indomethacin-related toxicity. Current evidence does not support this practice (Brion & Campbell, 2001). Surgical closure is undertaken when medical intervention fails or is contraindicated (Malviya, Ohlsson, & Shah, 2008; Wyllie, 2003).

Nursing care of the ELBW infants includes assessing, documenting, and reporting clinical signs of PDA such as bounding pulses, increased heart rate, and increasing pulse pressure (Koch et al., 2006). Nurses should monitor trends in oxygenation requirements and ventilation support in order to promote timely identification of infants with worsening pulmonary status. Reviewing weekly patterns will ensure that subtle increases in oxygen or ventilation needs over the course of a few days are not missed. Recording when radiographic examination(s) or echocardiograms have been ordered and completed will ensure findings are interpreted and treatment decisions are made promptly. Nurses should be familiar with contraindications of pharmacologic treatments for PDA to prevent or reduce risk of harm. ELBW infants receiving treatment should be monitored for oliguria, evidence of active gastrointestinal bleeding, platelet dysfunction, and spontaneous intestinal perforation. As such, clinical or biochemical (e.g., creatinine) changes should be reported, as this will assist the medical team to modify treatment regimens in ELBW infants experiencing complications secondary to treatment.

Hypotension

There is no uniform definition of hypotension in neonates. In research studies, hypotension is defined as any value that falls below the 5th or 10th percentile for gestational age and postnatal age (Kent & Chaudhari, 2013; Zubrow, Hulman, Kushner, & Falkner, 1995). Hypotension clinically manifests as low blood pressure, reduced cutaneous perfusion, and metabolic acidosis (Osborn & Evans, 2004). It is unclear what drop in blood pressure constitutes hypotension in ELBW infants (Ambalavanan & Whyte, 2003); hence, the threshold for treatment with crystalloids or cardiotropic medications varies among clinicians (Sehgal, 2011). A recent prospective study of infants born at less than 28 weeks' gestational age showed that hypotension in the first 24 hours following birth was not associated with ultrasound findings, suggesting cerebral white matter damage and diagnosis of cerebral palsy at 24 months CA (Logan et al., 2011). ELBW infants with hypotension but prior to treatment were found to have similar cerebral blood flow velocity as infants in the control group matched for gestational age and birth weight that had normal blood pressure (Lightburn, Gauss, Williams, & Kaiser, 2009). Sehgal (2011) asserts that hypotension alone may not reduce perfusion of organs such as the brain, heart, kidneys, and gastrointestinal system in ELBW infants.

Strategies for management of hypotension include volume expansion, inotropes, or corticosteroids (Osborn & Evans, 2004). Generally, corticosteroids are used as a last-chance therapy in managing hypotension (Ibrahim, Sinha, & Subhedar, 2011). Use of corticosteroids is supported based on our current understanding of pathophysiology (e.g., adrenocortical insufficiency, lower levels of cortisol concentration; Ibrahim et al., 2011; Sasidharan, 1998). In preterm infants without cardiovascular compromise, evidence does not support the routine use of early volume expansion (Osborn & Evans, 2004). Dopamine has been shown to be more effective than albumin (Osborn & Evans, 2004) and dobutamine (Subhedar & Shaw, 2003), but no firm recommendations can be made, as there is a paucity of evidence regarding effects on systemic oxygen delivery or cerebral perfusion and long-term benefit of dopamine (Barrington, 2011; Osborn & Evans, 2004; Subhedar & Shaw, 2003). According to Barrington (2011), the extremely low gestational age newborn (ELGAN) study published by O'Shea et al. (2009) demonstrates that treatment for hypotension (i.e., fluid boluses or inotrope/vasopressors) was not guided by the degree of illness or degree of hypotension but rather by "fashion and taste" (p. F317). Barrington (2011), based on the review of recent publications on hypotension in ELBW including the Logan et al. (2011) study, concluded:

- Many infants with low blood pressure have normal systemic flow.
- There is no clear evidence that infants with numerically low blood pressures but without evidence of shock have worsened outcomes.
- There is no evidence that treating numerically low blood pressures improves outcomes.
- There is no evidence base to determine the choice of one intervention over another (p. F317).

According to Sehgal (2011), in ELBW infants, multiple factors may contribute to hemodynamic instability (e.g., PDA, pulmonary vascular resistance, and myocardial function); as such, a varied approach to care may be more appropriate than consensus-based protocols. "A physiology-driven approach" framework is proposed using point-of-care echocardiography that will permit assessment of the ductus arteriosus, the muscles of the heart, and pulmonary and systemic hemodynamics. **Quality and Safety: Together with clinical context, this approach will help clinicians identify the etiology of cardiovascular compromise and permit individualized treatment decisions for ELBW infants** (Sehgal, 2011). Since clinical context will continue to be an important marker, nurses must systematically assess the ELBW infants' cardiovascular health by monitoring heart rate, capillary refill time, blood pressure, difference in pulse pressure, quality of pulses (i.e., bounding), presence of murmur(s), and precordial activity.

Fluid and Electrolytes

In ELBW infants, the first days after delivery are characterized by fluid shifts resulting from both physiologic changes and pathophysiologic events. "Physiologic weight reduction," the contraction of the extracellular compartment of body water, can be exacerbated as a result of insensible water loss (water lost from skin surface and the respiratory tract) and sensible water loss (water lost through urine and stool). Insensible water losses are extremely high and variable, making it challenging to predict total fluid intake. Given that the ELBW infant's kidneys have limited ability to compensate for varying water and solute intake (i.e., to adjust the concentration of urine), dehydration, fluid overload, and electrolyte imbalance are common events during the immediate postnatal period (Bell & Acarregui, 2008; Gaylord, Wright, Lorch, Lorch, & Walker, 2001; Lorenz, Kleinman, Ahmed, & Markarian, 1995).

A Cochrane systematic review concluded that restricted water intake in which physiologic needs are met reduced risk of PDA and NEC but increased postnatal weight loss. Since there was a trend toward an increased risk of dehydration, although the difference was not significant, it would be important to monitor infants closely for dehydration. **Emergency Alert: Certain complications such as BPD, IVH, and adverse events such as death were reduced with restricted fluid intake, though differences were not statistically significant when compared with liberal fluid intake** (Bell & Acarregui, 2008). Since ELBW infants were not well represented in this systematic review, a restrictive fluid management strategy cannot be universally applied to ELBW infants (Bell & Acarregui, 2008).

Some NICUs use swamping (piping highly humidified air into the isolette) when the infant is under a radiant warmer in an effort to reduce insensible water losses and promote thermoregulation. Incubators with the ability to regulate and deliver precise levels of humidification have been introduced in the NICU with the aim of reducing transepidermal water loss. Retrospective studies revealed that using humidified incubators in ELBW infants led to improved fluid management (Gaylord et al., 2001; Kim, Lee, Chen, & Ringer, 2010). High humidity is often provided to reduce water loss; however, the optimal level and duration of humidity remains unknown (Sinclair & Sinn, 2009). **Emergency Alert: High humidity may increase the risk of nosocomial infection in ELBW infants who are already compromised. New incubators have advanced systems of humidification (e.g., sterile humidity in gaseous vapor state) to minimize risk of infection.** High humidity may decrease the amount of light energy or irradiance delivered by phototherapy devices and thus may reduce the efficacy of phototherapy treatment (de Carvalho, Torrao, & Moreira, 2011).

Fluid requirements of ELBW infants must be monitored closely by nurses, as fluid disturbances can affect overall risk of death (Bell & Acarregui, 2008) and exacerbate morbidities such as PDA, congestive heart failure (Bell, Warburton, Stonestreet, & Oh, 1980), NEC, and BPD (Bell & Acarregui, 2008). **Quality and Safety: Daily weights, regular monitoring of electrolytes, strict documentation of fluid intake and output, cumulative fluid balance recordings, and graphic trends of growth should be maintained to facilitate decisions related to fluid management in ELBW infants.** ELBW infants receiving high humidity, as well as those receiving phototherapy, should be observed closely for signs and symptoms of infection. The irradiance of light should be monitored on an ongoing basis to ensure effectiveness of phototherapy treatment.

Metabolic Considerations

In ELBW infants, maintaining normoglycemia is difficult because of insufficient glycogen stores, stress, high metabolic rates, and variability in fluid requirements. Parenteral nutrition further elevates the risk of hyperglycemia and hypoglycemia in ELBW infants (Arsenault et al., 2012). **Emergency Alert: Hyperglycemia has been associated with increased risk of death** (Hays, Smith, & Sunehag, 2006; Kao et al., 2006), **IVH** (Hays et al., 2006), **NEC, late-onset sepsis** (Kao et al., 2006), **and prolonged hospital stay** (Hays et al., 2006). Routine use of insulin infusions to prevent hyperglycemia reduced the risk of hyperglycemia in VLBW infants, as well as ELBW infants. However, the systematic review concluded that given the increased risk of death before 28 days and hypoglycemia, routine use of insulin infusion to prevent hyperglycemia is not recommended (Sinclair, Bottino, & Cowett, 2011). At present, there is no consensus regarding cutoff values for hypoglycemia, or any strong evidence to provide guidance about specific approaches to treatment (Arsenault et al., 2012). **Quality and Safety: A blood glucose concentration persistently less than 36 mg/dL (2.0 mmol/L) or, in a symptomatic infant, a blood glucose concentration less than 45 mg/dL (2.5 mmol/L) is considered an indication for clinical intervention** (Cornblath et al., 2000; Kalhan & Devaska, 2011). If an infant has low blood sugar and requires intravenous glucose, it is preferable to administer 10% dextrose slowly at 2 mL/kg in order to reverse the hypoglycemia. Rapid or high-concentration boluses are not advisable, because rebound hypoglycemia can occur. There are a number of additional causes of hypoglycemia that may need individualized management (e.g., hyperinsulinism). Clinical management of hypoglycemia and hyperglycemia with devices such as the continuous glucose-monitoring sensor may prove beneficial in ELBW infants but still needs more validation in NICUs (Beardsall, Ogilvy-Stuart, Ahluwalia, Thompson, & Dunger, 2005). In a recent guideline for the management of hypoglycemia in newborns from the Canadian Neonatal Network, it has been recommended that asymptomatic, at-risk babies receive at least one effective feed before a blood sugar check at 2 hours of age, every 3 to 6 hours after this, and should be encouraged to feed regularly (Aziz, Dancey, & Canadian Paediatric Society, Fetus and Newborn Committee, 2004). **Quality and Safety: At-risk babies with regular feeding who repeatedly have low blood sugar of less than 2.6 mmol/L should be considered for intravenous therapy** (Aziz et al., 2004). Blood sugar testing may be discontinued after 12 hours in large for gestational age (LGA) infants and in infants of diabetic mothers if blood sugar levels remain at greater than or equal to 2.6 mmol/L. In SGA and preterm infants, once the feeding is established and blood sugar remains at 2.6 mmol/L or higher for 36 hours, there is no need to continue blood sugar estimation.

Nutrition

In ELBW infants, endogenous nutritional stores are limited as their bodies are primarily water. These endogenous nutritional stores are quickly depleted under conditions of starvation as metabolic needs are high. As a result, early nutrition is imperative to ensure the infants' continued survival. Nourishing ELBW infants is an important clinical concern, particularly in the first weeks of life, as significant nutritional deficits (e.g., protein and energy) may accrue over the hospitalization, resulting in postnatal or extrauterine growth restriction (Ehrenkranz, 2010; Ehrenkranz et al., 2006; Embleton, Pang, & Cooke, 2001). Early patterns of growth have been shown to have an independent effect on growth and neurodevelopment, including cognition and behavior (Ehrenkranz et al., 2006; Stephens et al., 2009; Ziegler, Thureen, & Carlson, 2002). ELBW infants are at an increased risk for poor somatic growth, with the poorest growth being seen in those infants who have comorbidities (e.g., feeding problems, respiratory illness, neurologic and developmental difficulties; Wood et al., 2003). **Emergency Alert: Malnutrition also impacts the structure**

(e.g., reducing number of replication cycles, reducing total brain DNA and connections between neurons and limiting arborization) and function (e.g., neurotransmitter levels) of the brain and development of the retina (Uauy & Mena, 2001).

Although little is known about the optimal requirement and quality of nutrition, nutritional goals for ELBW infants include weight gain that is similar both in rate and composition to the normal fetus at the same PMA (Adamkin, 2006). Early aggressive nutrition, defined as providing nutrition at or beyond the established standards (Ziegler et al., 2002), has been the focus in hopes of promoting adequate nutrition and limiting the negative consequences associated with nutritional deficits. Given that ELBW infants may be slow to tolerate the introduction of enteral feeds because of delayed gastric emptying and immaturity of intestinal motor activity, aggressive parenteral nutrition should be established soon after birth (within a few hours; Ziegler et al., 2002). Parenteral nutrition with 2.5 to 3.0 g/kg/day protein intake should be the target, with a stepwise increase commencing when energy intakes reach 70 kcal/kg/day. Protein requirement of about 4 g/kg/day is believed to be physiologic, and increased blood urea nitrogen suggests effective utilization of amino acids and is in keeping with the high fetal urea productions noted in the human fetus (Adamkin, 2006; Ziegler et al., 2002). However, this higher amount of protein is necessary when enteral nutrition is not provided for long periods of time and should be used with care as efficacy and safety have not been examined in a systematic way (Ziegler et al., 2002). Provision of high-protein and energy intake to ELBW infants was shown to limit catabolism and improve both growth and neurodevelopmental outcomes in ELBW infants (Maggio et al., 2007; Stephens et al., 2009).

Intravenous lipids should be commenced within 24 hours of birth as this provides essential fatty acids and an exogenous source of long-chain polyunsaturated fatty acids. ELBW infants are prone to essential fatty acid deficiency as they have little adipose tissue at birth and are unable to produce adequate amounts of long-chain polyunsaturated fatty acids (Uauy & Mena, 2001; Ziegler et al., 2002). Twenty percent lipid emulsion should be started by 24 hours of age, usually at a rate of 0.5 to 1 g/kg/day and increased by 0.5 g/kg/day every 24 to 48 hours up to 3 g/kg/day while monitoring triglyceride levels. Although lipid emulsions can displace bilirubin from albumin-binding sites, slow infusion rates (<150 mg/kg/hour) combined with slow increases in stepwise fashion to 3.0 g/kg/day should limit adverse effects (Ziegler et al., 2002). Aggressive intake of amino acids and intralipid administration of 3.5 g/kg/day of amino acids and 3 g/kg/day of intralipid are being advocated immediately after birth (within 1 hour) in VLBW infants and have been shown to be effective and safe (Ibrahim, Jeroudi, Baier, Dhanireddy, & Krouskop, 2004).

Use of trophic feeding or minimal enteral nutrition, defined as small-volume feeding of less than 24 mL/kg/day shortly after birth, is intended to achieve a biologic effect on the gastrointestinal system of VLBW infants in whom nutritional feeding is delayed (Bombell & McGuire, 2009). Although trophic feeding is well supported based on our understanding of the anatomic and physiologic disadvantages of delaying feeding (Premji, Paes, Jacobson, & Chessell, 2002), there is insufficient evidence regarding beneficial or harmful effects to make recommendations to inform clinical practice. Initiating trophic feedings within 48 hours of birth permits assessment of physiologic stability in ELBW infants (Premji et al., 2002). For ELBW infants, the continuous tube feeding method may be more energy efficient, as a subgroup analysis of infants included in a systematic review suggested that infants weighing less than 1,000 g gained weight significantly faster when fed by this method (Premji & Chessell, 2011). Further research is required to discern the benefits and risk of continuous tube feeding methods in ELBW infants.

Feeding ELBW infants while on noninvasive ventilation is challenging as evidence from clinical trials is lacking. However, in a recent observational quality improvement study, it was found that "Safe Individualized Nipple-Feeding Competence" (SINC) is feasible in ELBW and VLBW infants (Dalgleish, Kostecky, & Blachly, 2016). Using this SINC algorithm, 38% and 26% of the infants on the study received their first breastfeed or bottlefeed, respectively, while on nasal CPAP (Dalgleish et al., 2016).

ELBW infants are at increased risk of NEC, and earlier studies have demonstrated an association between timing of enteral feeding and rapid increases in feedings and NEC. Current evidence provides limited guidance regarding the effect of delayed (i.e., no advancement in first 5 days) versus earlier progression of feeding beyond trophic feeds on clinical outcomes in VLBW infants (Morgan, Young, & McGuire, 2014). Furthermore, slow advancement of feedings (i.e., 15–20 mL/kg) in VLBW infants results in delay in regaining birth weight and reaching full enteral feedings and does not reduce the risk of NEC. Numerous detrimental effects of total parenteral nutrition are cited in the literature, including metabolic complications, infection, and changes in the structural integrity and function of the gastrointestinal system. Consequently, more studies need to examine advancing feeding volumes in ELBW infants. Given that information regarding safety is unclear, a feeding advancement of not more than 30 mL/kg/day has been advocated (Premji et al., 2002). Refinement of feeding strategies that facilitate quick transition from parenteral to minimal enteral nutrition to progressive enteral nutrition and advancement of feedings that meet the specific needs of ELBW infants should be the focus of future research.

Human milk is considered the best feeding substrate for premature infants as it confers biologic (e.g., easier to digest and absorb), immunologic (e.g., lower rate of infection and incidence of NEC), and developmental (e.g., improved intelligence quotient) advantages (Lucas & Cole, 1990; Lucas, Morley, Cole, Lister, & Leeson-Payne, 1992; Schanler, 1995). A cohort study of 1,035 ELBW infants reported higher MDI scores at 18 months CA in infants who received more breast milk versus formula during hospitalization in the NICU (Vohr et al., 2006). However, preterm human milk does not have sufficient quantities of protein, sodium, phosphate, and calcium to meet estimated needs for growth. Fortification of human milk is therefore essential to maintain adequate growth, nutrient retention, and biochemical homeostasis (Atkinson, 2000; Schanler, 1995). Commercially available fortifiers come in liquid or powder form. Potential complications of fortification include distended abdomen, increased osmolarity, and bacterial contamination. In a systematic review, protein supplementation of human milk in relatively healthy preterm infants resulted in short-term growth; however, the adverse effects of protein supplementation could not be discerned (Kuschel & Harding, 2000). Nurses can support mothers to express breast milk soon after birth, as well as assist mothers to maintain adequate milk supply by encouraging mothers to pump at least 8 to 12 times in a day. Strategies such as kangaroo care, which may facilitate milk production and growth of the infant, should be routine aspects of care.

Currently, there is controversy with respect to concurrent feeding and indomethacin therapy. The reduced mesenteric diastolic blood flow associated with indomethacin therapy may be counteracted by minimal enteral nutrition, thereby exerting a protective influence on the gastrointestinal system. However, clinical practice varies between units, with some following the conventional wisdom of withholding enteral feeding during indomethacin therapy to prevent NEC (Premji et al., 2002). A recent randomized controlled trial showed that infants who were receiving indomethacin or ibuprofen treatments and also receiving trophic enteral

feeds required less time to reach to the feeding volume endpoint (Clyman Pediatrics, 2013).

Patole and de Klerk (2005) propose that clinical variation in practice determines risk of NEC. Neonatologists' lack of comfort with initiating and advancing protein and energy intake contributed to significant differences in practices, despite instituting guidelines for aggressive protein and energy intake (Stephens et al., 2009). Nursing management of feeding is also inconsistent, and variability in the practice of withdrawing feeding and management of feeding residuals (Hodges & Vincent, 1993) and selection of feeding route (e.g., nasogastric vs. orogastric) (Birnbaum & Limperopoulos, 2009) has been shown. A better understanding is required of nursing practice related to tube feeding in order to facilitate a standardized systematic evidence-based approach founded on the current state of scientific knowledge (Premji, 2005).

Physiologic, behavioral, and neurologic immaturity contributes to feeding problems experienced by ELBW infants. **Quality and Safety: A prerequisite to safe and successful oral feeding is effective sucking behavior and intact gag and cough reflexes** (Medoff-Cooper & Ray, 1995; Shaker, 1990). Transitioning ELBW infants from tube feeding to oral feeding is a major challenge for nurses, as no criteria exist to guide practice (Hawdon, Beauregard, Slattery, & Kennedy, 2000; Pickler & Reyna, 2003), and hence the practice is variable and based on custom (McCain, Gartside, Greenberg, & Lott, 2001). An evidence-based neonatal oral feeding protocol has been developed to create positive feeding experiences while assisting high-risk infants to achieve full oral feedings (Premji, McNeil, & Scotland, 2004). Infant characteristics (not postconceptional age) are the primary determinants used to plan physiologically appropriate feeding experiences for each stage—preoral stimulation, nonnutritive sucking, and nutritive sucking—of progression to oral feeding. The mainstay of this protocol is a professional resocialization in the way nurses view and engage in feeding interactions, with emphasis on the quality of the feeding interaction rather than the quantity of milk consumed by the infant. For continued improvement in nutritional management of ELBW infants, it is imperative that nurses engage in protocol appraisal and self-appraisal of practice, and that they review new evidence.

Gastroesophageal Reflux

Another complication related to digestion is GER disease, a maturational phenomenon caused by transient lower esophageal sphincter relaxation (Ambalavanan & Whyte, 2003; Omari et al., 2004). Placement of a feeding tube across the gastroesophageal junction has been shown to increase the incidence of GER (Peter, Wiechers, Bohnhorst, Silny, & Poets, 2002). Other factors that may influence the presence of GER include supine position and large volume of fluid intake. Clinical signs of GER include visible regurgitation, and infants may cry, be irritable, or have altered sleeping patterns (e.g., remain awakened; Poets & Brockmann, 2011). GER is also considered a risk factor for aspiration and subsequent pneumonia (Ambalavanan & Whyte, 2003). The association between BPD and GER is thought to be due to greater diagnostic suspicion in infants with chronic lung disease (Fuloria, Hiatt, Dillard, & O'Shea, 2000; Poets & Brockmann, 2011). GER does not appear to increase the risk of delayed growth (<10th percentile) or development (Bayley Mental Developmental and Psychomotor Developmental Indices of <70) in VLBW infants (Fuloria et al., 2000). GER is considered pathologic based on the quality rather than quantity of the refluxate (Poets & Brockmann, 2011). GER is difficult to diagnose, as current techniques of esophageal pH monitoring cannot reliably detect GER in preterm infants. This is because frequent feeding causes esophageal acidification to pH less than 4 (Grant & Cochran, 2001; Omari et al., 2004). Consequently, the contribution of GER to neonatal morbidity and the efficacy of therapies for GER are difficult to evaluate.

The association between GER and AOP is biologically plausible as the refluxate can stimulate laryngeal chemoreceptors; hence, it is not surprising that studies (Omari, 2009) have demonstrated a relationship between GER and apnea. There are studies (Peter, Sprodowski, Bohnhorst, Silny, & Poets, 2002) that also show no temporal relationship between apnea and GER in preterm infants (Peter, Sprodowski, et al., 2002). Poet and Brockmann (2011) concluded, given the lack of consistent evidence and the fact that antireflux medications have not been useful in managing AOP, that apneas are not related to GER.

At present, there is lack of consensus with regard to optimal management of GER in ELBW infants, as there are few randomized controlled trials to guide practice (El-Mahdy, Mansoor, & Jadcherla, 2017). Pharmacologic measures (e.g., metoclopramide, domperidone; Ambalavanan & Whyte, 2003) should be used sparingly, as the consequence of GER remains to be established in ELBW infants (Poets & Brockmann, 2011). Though prokinetic reflux medications improve the lower esophageal sphincter basal pressure, lower esophageal peristalsis, and increase esophageal acid clearance and gastric emptying, they have some adverse effects including ventricular arrhythmias, extrapyramidal effects, and prolonged QT interval especially with domperidone (El-Mahdy et al., 2017). The use of metoclopramide is now obsolete in neonatology due to its side effects such as dystonic and dyskinetic reactions (El-Mahdy et al., 2017). It is advisable to perform ECG before and after starting domperidone in neonates to assess for prolonged QT interval and associated arrhythmias. The use of H_2 receptor antagonist and proton pump inhibitors for a long time period may cause serious side effects such as bacterial colonization, community acquired pneumonia, diarrhea, and increased bone fractures (El-Mahdy et al., 2017). Prone and left lateral positioning have been shown to reduce the number and duration of reflux episodes (Corvaglia et al., 2007; Ewer, James, & Tobin, 1999).

Anemia

The primary cause of anemia, particularly in the first 2 weeks of life, is phlebotomy losses resulting from intensive laboratory testing. Other causes include an inability to increase erythropoietin concentration and erythropoiesis, and severely limited blood volume based on body weight (Ohls, 2002). In the preterm infant, typically there is a physiologic fall in hemoglobin and hematocrit levels by approximately 6 weeks of age. The decline in hematocrit in ELBW infants is associated with clinical findings necessitating packed red blood cell transfusion, and hence is not considered "physiologic" (Aher & Ohlsson, 2014). It is uncertain what hematocrit levels precipitate clinical signs of anemia of prematurity and what is the minimal acceptable level for infants requiring ventilatory support (Ohls, 2002). Low hemoglobin and hematocrit levels often guide decisions regarding blood transfusion (Aher & Ohlsson, 2014). Based on the premature infants in need of transfusion (PINT) study and a Cochrane review, the need for transfusion should be based on the individual targets for patient's health rather than based on using low threshold hemoglobin levels (Kirpalani et al., 2006; Whyte & Kirpalani, 2011). Neither study found any difference in the outcomes (death or disability) based on the low threshold criteria (Kirpalani et al., 2006; Whyte & Kirpalani, 2011). As a result of more stringent transfusion guidelines (i.e., lower threshold for transfusion), the number of blood transfusions have decreased over the past decade (Maier et al., 2000). No statistically significant differences were noted in death

or neurodevelopmental impairment between those maintained at low hemoglobin levels (i.e., restrictive) versus those with high hemoglobin levels (i.e., liberal). Although infants in the restrictive group had lower hemoglobin levels in the first few weeks of life, at 18 months CA, these differences were no longer evident (Whyte et al., 2009). Post hoc analysis, however, revealed significantly higher rates of cognitive delay (i.e., MDI score <85) in the restrictive hemoglobin group (Whyte et al., 2009). In contrast, a retrospective study of ELBW infants revealed that the number of blood transfusions was significantly associated with severity of ROP (Englert, Saunders, Purohit, Hulsey, & Ebeling, 2001). Other benefits of reducing the number of packed red blood cell transfusions include reduced risk of transmission of viral infections, reduced risk of incompatibility, and reduced cost (Aher & Ohlsson, 2014).

Delayed cord clamping (DCC, optimally for 30–180 seconds) for preterm infants has some beneficial effects, especially reducing the number of blood transfusions these infants require (Lemyre, Sample, Lacaze-Masmonteil, & Canadian Paediatric Society, 2015). In a systematic review and meta-analysis of DCC versus immediate cord clamping (ICC) in preterm infants, Fogarty et al. (2018) found that infants who were in the DCC group received 10% less blood transfusions compared to those in the ICC group.

A meta-analysis reported that administration of recombinant erythropoietin in the first week of life resulted in a moderate reduction in the proportion of VLBW infants requiring blood transfusion. Subgroup analysis revealed that ELBW infants were less likely to avoid transfusion if treated with recombinant erythropoietin (Kotto-Kome, Garcia, Calhoun, & Christensen, 2004). As per Canadian Pediatric Society recommendations, routine use of erythropoietin is not recommended (Lemyre, Sample, Lacaze-Masmonteil, & Canadian Pediatric Society, Fetus and Newborn Committee, 2015). A recent Cochrane systematic review also concluded that early erythropoietin, that is, administration of erythropoietin before 8 days of age, is not recommended as there is no strong evidence for its neuroprotective role: no impact on mortality, limited clinical importance of reduction in blood cell transfusions, volume of red blood cells transfusions, and significant increase in the rate of ROP (stage ≥3; Aher & Ohlsson, 2014). Consequently, strategies or interventions (e.g., point-of-care devices) that reduce phlebotomy losses and blood transfusions throughout the infant's hospital stay warrant further investigation (Madan et al., 2005; Moya, Clark, Nicks, & Tanaka, 2001). Additionally, the nurse can act as an advocate to eliminate unnecessary laboratory monitoring.

Infection

Infections are frequent complications of ELBW infants, with approximately 50% to 65% of infants having at least one infection during hospitalization. There are multitudes of nonspecific signs and symptoms of sepsis, namely, temperature instability, apnea and bradycardia, feeding intolerance, abdominal distention, lethargy, septic shock, and increased need for oxygen or ventilatory support (Craft, Finer, & Barrington, 2000). Infection rates increase with decreasing birth weight and gestational age and are associated with increased mortality and poor neurodevelopmental and growth outcomes in childhood (Schlapbach et al., 2011; Stoll et al., 2004; Tolsma et al., 2011). The ELGAN study, which followed 1,059 infants born at less than 28 weeks' gestational age, identified definite late neonatal bacteremia as an independent risk factor for ROP (Tolsma et al., 2011).

Early-onset infection (before 72 hours) is due to maternal factors (congenital) and is uncommon, but can be life threatening (Ambalavanan & Whyte, 2003). Risk of early-onset sepsis (e.g., *group B streptococcal* infection) may be decreased with intrapartum antibiotic prophylaxis, but there is concern that it may mask infection, with onset of signs of sepsis taking longer. In almost all ELBW infants, antibiotics (ampicillin or penicillin and aminoglycoside) for suspected sepsis are initiated after birth, and if the infant is asymptomatic and culture is negative, antibiotic therapy is discontinued after 48 to 72 hours. It is unclear what impact the frequent and empiric use of antibiotics has on the incidence and resistance pattern of late-onset bacterial infection (Ambalavanan & Whyte, 2003). Prior use of broad-spectrum antibiotics has been associated with invasive candidiasis, which in ELBW infants may be fatal, ranking second among the leading causes of infection-related deaths in ELBW infants (Benjamin et al., 2010). A recent study indicated that just by observing clinical presentations in neonates as a part of the management, the need for antibiotics in chorioamnionitis-exposed infants has been dramatically reduced (Joshi et al., 2018). Guidelines for early-onset sepsis recommending limited use of broad-spectrum antibiotics, as well as reduced duration of treatment, were found to be effective (i.e., did not "increase the risk of infectious relapse") when implemented for infants less than 35 weeks' gestational age, as well as near-term and term infants. Their efficacy and safety need to be established in ELBW infants (Labenne, Michaut, Gouyon, Ferdynus, & Gouyon, 2007). The use of a web-based sepsis risk calculator in the daily clinical practice in NICU may significantly reduce the use of antibiotics and laboratory testing in the early-onset sepsis and may prevent antibiotic-resistant organisms (Dhudasia, Mukhopadhyay, & Puopolo, 2018). After use of this calculator, empirical antibiotics use among newborns within 72 hours of life has dramatically decreased by 42% and laboratory testing declined by 82% (Dhudasia et al., 2018). The use of biomarkers including procalcitonin and interleukin-8 have greater than 80% predictability in detecting early-onset sepsis (Nakstad, 2018). However, these markers are not routinely used in the modern NICUs due to various feasibility and budgetary reasons.

Late-onset sepsis (after 72 hours), referred to as nosocomial infection, is an acquired infection with *coagulase-negative staphylococci* being the most common cause of bacteremia (Craft et al., 2000). According to Craft et al. (2000), the risk of acquired infection is high because ELBW infants have an immature immune system; they often lack the protection of passive immunity, they have poor epidermal and gastrointestinal barrier function, and they may have central arterial or venous catheters (e.g., umbilical lines and percutaneous central venous catheters). In a large prospective cohort study, infections among ELBW infants were associated with poor neurodevelopmental outcomes (Cerebral palsy; range of odds ratios [Ors: 1.4–1.7], MDI [Ors: 1.3–1.6], and PDI [Ors: 1.5–2.4]) and poor growth outcomes at 18 to 22 months CA (Stoll et al., 2004). In another study, preterm infants born at less than 28 weeks' gestational age who had late-onset sepsis during postnatal weeks 2 to 4 have been shown to be at higher risk of low IQ at school age (Bright et al., 2017). The adverse long-term outcomes in preterm infants with sepsis with other morbidities like NEC or BPD may become higher compared to sepsis alone (Adams-Chapman, 2012).

Evidence-based practices that prevent or control the spread of bacterial and viral infections such as hand hygiene are not always adhered to in practice. These variations in practice may explain the different rates of infection reported in the literature by different NICUs (Higgins, Baker, & Raju, 2010). In ELBW infants, oral lactoferrin may reduce the incidence of late-onset sepsis (Pammi & Abrams, 2011), while pentoxifylline given as an adjunct to antibiotic treatment may reduce mortality without adverse effects (Haque & Pammi, 2011), but more research is required before these strategies can be routinely adopted in practice. Similarly, vancomycin for prophylaxis against sepsis has been found to be

effective in reducing the incidence of sepsis, although further research is required as organisms may develop resistance to vancomycin (Craft et al., 2000).

Skin breakdown, another pathway for infection, occurs more frequently in ELBW infants, and it is proposed that topical ointment therapy may serve as a protective barrier leading to improved skin integrity and a decreased risk of nosocomial infection (Conner, Soll, & Edwards, 2004). **Quality and Safety: Application of a preservative-free emollient ointment improves skin condition and reduces transepidermal water loss, but is associated with adverse outcomes.** The risk of *coagulase-negative staphylococcal* infection and any nosocomial infection (e.g., bacterial and fungal organism) increased with the application of ointment (Conner et al., 2004). Other potential strategies to minimize skin breakdown, thereby reducing the risk of infection, include use of as little tape as possible, and changing the infant's position frequently to prevent abrasions and pressure areas. It is important to remember that other treatments, procedures, and conditions may aggravate the problem (e.g., steroid therapy; use of blood products, leading to thrombocytopenia or lymphocytopenia; invasive procedures; changes in the pH of the skin as a result of bathing practices). Renal function is compromised in ELBW infants. It is imperative that nurses give medications (particularly nephrotoxic drugs such as gentamicin) with careful consideration of renal function. If renal function is compromised, a toxic level of this drug can be reached quite quickly, leading to permanent renal and auditory damage. The nurse should consider where the drug is metabolized and cleared through the body. If the site is the renal system and if output is severely diminished, use of the medication may need to be suspended temporarily.

Given the spectrum of issues that may be encountered by an ELBW infant, an individualized approach to care is crucial. Consistent and sound clinical reasoning based on history and physical examination, comprehensive data (e.g., essential laboratory findings), and knowledge (e.g., research evidence) should guide nursing practice decisions. Moreover, parents' wishes should be considered in making judgments about best practices, as they hold the ultimate moral and legal authority to make decisions about the infant's treatment. The ethical imperative is shared decision making (Penticuff & Arheart, 2005).

FAMILIES OF ELBW INFANTS

The birth of an ELBW infant generates a cascade of parental emotions and fears beginning with decisions related to resuscitation and to uncertainty regarding survival of the infant (Sydnor-Greenberg & Dokken, 2000). An interpretive phenomenologic analysis of mothers' lived experience of giving birth to an ELBW infant revealed that "being the mother" entailed being worried and scared about the uncertainty of the outcome and thinking the worst (Schenk & Kelley, 2010). Parental grief over the death of an ELBW infant, loss of a desired child, loss of pregnancy, or past losses may be adversely influenced by external factors. Nursing behaviors can influence this grief, which is a multidimensional complex process (Golish & Powell, 2003; Sydnor-Greenberg & Dokken, 2000).

Effective communication that incorporates support (physical or social) and teaching will assist parents to find their own unique paths to meaningful involvement (Sydnor-Greenberg & Dokken, 2000). It is important that nurses realize that there will be individual differences depending on the race, religion, nationality, and cultural background of the families. Although it may seem daunting at times, nurses should attempt to accurately interpret and respond to various behaviors by parents to facilitate meaningful involvement in caring for their infant (Sydnor-Greenberg & Dokken, 2000). Principles of family-centered care combined with principles of developmental care are an excellent framework to encourage families to participate as fully as possible in caring for and making decisions about their infant, and to form mutually beneficial and supportive partnerships in the NICU (Lester et al., 2011). A new family-centered program called Family Integrated Care (FICare) and its role in the NICU was recently studied in level III NICUs (O'Brien et al., 2017). The study empowered parents to become the primary caregivers to their infants and resulted in improved outcomes for both families and infants (O'Brien et al., 2017).

A crucial element in caring for ELBW infants is to engage families to participate collaboratively in deciding on appropriate care. The ability of the families to understand accurately their infant's medical condition, prognosis, and treatment options depends on the healthcare professional's ability to take a participatory approach to care (Penticuff & Arheart, 2005).

SUMMARY

This chapter presented a brief overview of the mortality and morbidities associated with being born ELBW, care required for the problems encountered by ELBW infants, and potential areas for future research. There are many unknowns; however, there is hope: a trust in the future of life. Nurses, physicians, other healthcare providers, and parents can make a difference if they are aware of the potential problems and know how to detect or recognize them early.

CASE STUDY

Michael was born at 23 weeks' gestational age by VD to a 23-year-old G2 P1 mother HBsAg-negative, VDRL nonreactive, GBS-negative after failed tocolysis × 3 hours. Apgars 2/8. Intubated and given surfactant in DR. Transported to NICU in incubator.

■ Admission Assessment

- GENERAL: 778 g, TPR: 96, HR 168, RR 60 (ventilated), BP 24
- SKIN: mottled, cool, extensive bruising on both legs
- HEENT: normocephalic, fontanelle soft and flat, palate intact
- NECK: no masses, clavicles intact
- LUNGS: BBS equal, coarse rales
- CV: RRR, no murmur, CFT 4 seconds
- ABD: soft, flat, liver palpable at RCM, UAC in place, two arteries, one vein visible
- GENITALIA: normal preterm male genitalia, patent anus
- EXT: moves all extremities, pulses × 4
- NEURO: poor tone, AGA 23 weeks
- IMPRESSION: 23-week, preterm AGA, male newborn with respiratory distress

■ Questions to Consider

What is the first differential diagnosis for Baby Michael?
Respiratory distress syndrome secondary to surfactant deficiency versus sepsis versus hypothermia
What will the initial management plan include?

1. Ventilatory support at lowest settings needed to maintain oxygenation; wean as possible using O_2 saturations and arterial blood gas (ABG)
2. Incubator with temperature and humidity control

3. IV fluids
4. Monitor blood pressure; consider bolus
5. Ampicillin and gentamicin
6. Talking to parents

What diagnostic tests will likely be ordered?

1. CBC with differential
2. Blood culture
3. ABG
4. Bedside glucose
5. Blood chemistries, bilirubin levels
6. Chest x-ray

On day 2 of life, Michael's parents ask you, "Is he going to be okay?" What would you tell them?

There is no answer to this question, because we don't know all the answers. That is a good way to begin your answer. The editors hope that reading this book will better prepare you to answer these and other questions.

EVIDENCE-BASED PRACTICE BOX

Use of Human Milk in the Early Neonatal Period

Human milk is recognized as the ideal nutrition for preterm neonates because of the protection it confers to ELBW infants through its biologic and immunologic properties (Higgins et al., 2012). For ELBW infants, prevention of NEC is important, as it is a leading cause of mortality and morbidity. Neonates fed human milk have lower rates of NEC overall and those who develop NEC have lower mortality and late-onset sepsis, compared to neonates fed preterm formula (Schanler, Lau, Hurst, & Smith, 2005; Vohr et al., 2007). Human milk has a dose–response relationship in reducing the risk of NEC in the first 14 to 28 days of life (Meinzen-Derr et al., 2009; Vohr et al., 2007). The amount of human milk received in early life is also related to health outcomes in later life (e.g., 30 months of age) in a dose–response fashion (Vohr et al., 2007). Slower weight gain in infants who were fed human milk did not preclude them from being discharged earlier (Schanler et al., 2005). Overall weight gain at 18 months was found to be no different in those receiving human milk when compared to those receiving formula in early life (Vohr et al., 2006). Human milk also reduces risk of atopy and rates of rehospitalization, and promotes developmental outcomes (Higgins et al., 2012; Vohr et al., 2007). Although donor human milk is associated with a lower risk of NEC when compared to formula feeding, no conclusions can be made given the quality of the evidence (Boyd, Quigley, & Brocklehurst, 2007).

References

Boyd, C. A., Quigley, M. A., & Brocklehurst, P. (2007). Donor breast milk versus infant formula for preterm infants: Systematic review and meta-analysis. *Archives of Disease in Childhood—Fetal and Neonatal Edition, 92*(3), F169–F175. doi:10.1136/adc.2005.089490

Higgins, R. D., Devaskar, S., Hay, W. W., Jr., Ehrenkranz, R. A., Greer, F. R., Kennedy, K., . . . Sherman, M. P. (2012). Executive summary of the workshop "Nutritional Challenges in the High Risk Infant." *Journal of Pediatrics, 160*(3), 511–516. doi:10.1016/j.jpeds.2011.12.024

Meinzen-Derr, J., Poindexter, B., Wrage, L., Morrow, A. L., Stoll, B., & Donovan, E. F. (2009). Role of human milk in extremely low birth weight infants' risk of necrotizing enterocolitis or death. *Journal of Perinatology, 29*, 57–62. doi:10.1038/jp.2008.117

Schanler, R., Lau, C., Hurst, N. M., & Smith, E. O. (2005). Randomized trial of donor human milk feeding versus preterm formula as substitutes for mothers' own milk in the feeding of extremely premature infants. *Pediatrics, 116*(2), 400–406. doi:10.1542/peds.2004-1974

Vohr, B., Poindexter, B., Dusick, A., McKinley, L. T., Higgins, R. D., Langer, J. C., & Poole, W. K. (2007). Persistent beneficial effects of breast milk ingested in the neonatal intensive care unit on outcomes of extremely low birth weight infants at 30 months of age. *Pediatrics, 120*(4), e953–e959. doi:10.1542/peds.2006-3227

Vohr, B., Poindexter, B. B., Dusick, A. M., McKinley, L. T., Wright, L. L., Langer, J. C., & Poole, W. K. (2006). Beneficial effects of breast milk in the neonatal intensive care unit on the developmental outcome of extremely low birth weight infants at 18 months of age. *Pediatrics, 118*(1), e115–e123. doi:10.1542/peds.2005-2382

PARENT VOICES

Jennifer Degl

What do nurses need to know about ELBW infants and their families? This is a very difficult question to answer because I have always felt as if I did not get to parent my micropreemie while she was in the NICU. I now know that I did what I could and I was parenting her as best that I could, given our situation. I did not get to hold her when she cried or feed her when she was hungry because my daughter (born at 23 weeks) had a feeding tube and went straight to the incubator after her birth. I was not able to touch her for a few days, and that's not what was "supposed" to happen. I had to

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sanitize my hands before I stuck my finger in the opening on the side of the incubator. Parents are meant to touch their baby for the first time in this manner. Parents of healthy newborns get to hold their baby immediately after birth and then hold them as much as possible. But that was not our reality. I was not able to hold my daughter for one month, with the first time lasting only a few minutes. Parenting a baby in the NICU depends on the baby's individual medical needs and the parents' cultural traditions and comfort level. For over a month, I would open up the portal on the side of the incubator and talk and sing to my daughter while I was there. At first, I would speak in a very quiet voice, as I was nervous and shy around the staff and other parents in the room, but gradually I relaxed and became more comfortable with the staff and my new home, and I would speak to her in a normal voice so that she knew I was there. I learned how to participate in her care activities, like taking her temperature and changing her diaper every few hours. Eventually she could come out of the incubator for feeds and I would hold the vial of breast milk while she "ate," although she was tube-fed for months. While I really did not do much myself, these simple acts allowed me to feel more like her mother. This was a very different type of parenting than how I parented my other children, but I did what I could. It's not easy. Once they are comfortable with the NICU environment, I would suggest that parents ask the nurses about ways they can be more involved in their baby's care. NICU nurses can be very creative and will involve parents in the care activities when they can. Sometimes they just have to ask. This will encourage happier and more involved parents and it will also foster feelings of bonding.

Jenny R. McCormick

Walking into the NICU and meeting my incredibly tiny baby for the first time is an experience I will never forget. The myriads of machines, wires, and alarms are not only overwhelming, but left me with the intense gut-wrenching fear that this fragile new life might not make it home. The most natural tasks such as holding your baby, soothing, and caring for him/her become unnatural as you learn to do all of these things in a sterile and oftentimes chaotic environment. Nursing staff need to remember that most parents walking into the NICU are not walking in with a medical degree. The sights, sounds, smells, and watching your child grow outside of you are not only overwhelming experiences but also traumatizing. The simple act of holding a micropreemie is incredibly scary. Learning how to advocate for your preemie and develop the NICU lingo takes time. Patience is key. Empathy is everything.

Jennifer M. Driscoll

Our daughter, Lilian Hope, was born 7 weeks premature, weighing only 2 lb 12 oz and 15 inches long. Lily's lungs were her main problem, as they are for many preemies, because the lungs are the last thing to develop. On the day she was born, she was doing well, but still needed a continuous positive airway pressure (CPAP) machine to help her breathe. As the day progressed, her condition worsened. She was given nitric oxide, put onto a ventilator to breathe for her, and an oscillator to vibrate the lungs to help the flow of oxygen. Due to the force of the ventilator and oscillator, an air sac in her lungs burst and she had a chest tube inserted. Additionally, she had an erratic blood pressure and jaundice and needed multiple blood transfusions.

I remember a few days into her NICU stay, one of the nurses offered for me to help change her diaper and I remember feeling so scared. I don't have siblings and it had been years since I was a babysitter. I knew I would have to change a diaper, but I assumed it would be a big, happy, healthy baby's diaper I would be changing. I felt like I didn't know what I was doing. How do I change her preemie diaper that was WAY too big for her? How do I do it around her wires and tubes? How do I not hurt her? I did it . . . and remember feeling a connection to her because it was my first "mom" experience. The miracle continued as she began to gain strength inside herself; she came off the oscillator after 7 days and took out the ventilator herself. By day 8, a nurse offered for us to hold her for the first time. This was an incredible day, yet frightening and overwhelming at the same time because she still had tubes and wires hanging from her. It was an amazing feeling holding her, and we celebrated with our first family picture together.

These two tiny gestures by her nurses created the pathway to helping me feel more confident not only as a new mother, but also as a new mother caring for a sick baby.

ONLINE RESOURCES

CAN- Neonatology. (2011). *John D. Lantos MD—ethical issues around the care of ELBW infants* [Veo file]. Retrieved from http://vimeo.com/20937433

CAN- Neonatology. (2011). *Neil Finder MD—CPAP vs. surfactant in the ELBW infant* [Video file]. Retrieved from http://vimeo.com/21309386

CAN- Neonatology. (2011). *Panel discussion on golden hour management of ELBW* [Video file]. Retrieved from http://vimeo.com/21319275

ELBW Follow-up. Retrieved from http://www.vtoxford.org/research/elbw/elbw.aspx

REFERENCES

Adamkin, D. H. (2006). Nutrition management of the very low-birth weight infant: II. Optimizing enteral nutrition and postdischarge nutrition. *Neoreviews*, *7*(12), e608–e614. doi:10.1542/neo.7-12-e608

Adams-Chapman, I. (2012). Long-term impact of infection on the preterm neonate. *Seminars in Perinatology*, *36*(6), 462–470. doi:10.1053/j.semperi.2012.06.009

Aher, S. M., & Ohlsson, A. (2014). Late erythropoietin for preventing red blood cell transfusion in preterm and/or low birth weight infants.

The Cochrane Database of Systematic Reviews, (4), CD004868. doi:10.1002/14651858.CD004868.pub4

Al-Alaiyan, S., Dawoud, M., & Al-Hazzani, F. (2014). Positive distending pressure produced by heated, humidified high flow nasal cannula as compared to nasal continuous positive airway pressure in premature infants. *Journal of Neonatal-Perinatal Medicine, 7*(2), 119–124. doi:10.3233/NPM-1474113

Albersheim, S. (2008). Ethical consideration at the threshold of viability. *British Columbia Medical Journal, 50*, 509–511. Retrieved from https://www.bcmj.org/articles/ethical-considerations-threshold-viability

Aldana-Aguirre, J. C., Pinto, M., Featherstone, R. M., & Kumar, M. (2017). Less invasive surfactant administration versus intubation for surfactant delivery in preterm infants with respiratory distress syndrome: A systematic review and meta-analysis. *Archives of Disease in Childhood—Fetal and Neonatal Edition, 102*(1), F17–F23. doi:10.1136/archdischild-2015-310299

Allendorf, A., Dewitz, R., Weber, J., Bakthiar, S., Schloesser, R., & Rolle, U. (2018). Necrotizing enterocolitis as a prognostic factor for the neurodevelopmental outcome of preterm infants—Match control study after 2 years. *Journal of Pediatric Surgery*, *53*(8), 1573–1577. doi:10.1016/j.jpedsurg.2018.01.006

Ambalavanan, N., & Whyte, R. K. (2003). The mismatch between evidence and practice: Common therapies in search of evidence. *Clinics in Perinatology, 30*(2), 305–331. doi:10.1016/S0095-5108(03)00021-6

Amer, R., Moddemann, D., Seshia, M., Alvaro, R., Synnes, A., Lee, K.-S., . . . Shah, P. S. (2018). Neurodevelopmental outcomes of infants born at <29 weeks of gestation admitted to Canadian neonatal intensive care units based on location of birth. *The Journal of Pediatrics, 196*, 31–37.e1. doi:10.1016/j.jpeds.2017.11.038

American Academy of Pediatrics, & American Heart Association. (2016). In G. M. Weiner & Jeanette Zaichkin (Eds.), *The Textbook of Neonatal Resuscitation* (7th ed.), Itasca, IL: Author

American College of Obstetricians and Gynecologists & Society for Maternal–Fetal Medicine. (2017). Obstetric care consensus No. 6: Periviable birth. *Obstetrics & Gynecology, 130*(4), e187–e199. doi:10.1097/aog.0000000000002352

Ancel, P.-Y., Goffinet, F., Kuhn, P., Langer, B., Matis, J., Hernandorena, X., . . . Kaminski, M. (2015). Survival and morbidity of preterm children born at 22 through 34 weeks' gestation in France in 2011: Results of the EPIPAGE-2 cohort study. *Journal of the American Medical Association Pediatrics, 169*(3), 230–238. doi:10.1001/jamapediatrics.2014.3351

Andersen, C. C., & Phelps, D. L. (2000). Peripheral retinal ablation for threshold retinopathy of prematurity in preterm infants. *The Cochrane Database of Systematic Reviews,* (2), CD001693. doi:10.1002/14651858.CD001693

Anderson, J. G., Baer, R. J., Partridge, J. C., Kuppermann, M., Franck, L. S., Rand, L., . . . Rogers, E. E. (2016). Survival and major morbidity of extremely preterm infants: A population-based study. *Pediatrics, 138*(1), e20154434. doi:10.1542/peds.2015–4434

Arsenault, D., Brenn, M., Kim, S., Gura, K., Compher, C., & Simpser, E., . . . & Puder, M. (2012). A. S. P. E.N. clinical guidelines: Hyperglycemia and hypoglycemia in the neonate receiving parenteral nutrition. *Journal of Parenteral and Enteral Nutrition, 36*(1), 81–95. doi:10.1177/0148607111418980

Askie, L., Henderson-Smart, D., & Ko, H. (2009). Restricted versus liberal oxygen exposure for preventing morbidity and mortality in preterm or low birth weight infants. *The Cochrane Database of Systematic Reviews,* (4), doi:10.1002/14651858.CD001077.pub2

Atkinson, S. A. (2000). Human milk feeding of the micropremie. *Clinics in Perinatology, 27*(1), 235–247. doi: 10.1016/S0095-5108(05)70016-6

Austeng, D., Källen, K. B., Ewald, U. W., Jakobsson, P. G., & Holmström, G. E. (2009). Incidence of retinopathy of prematurity in infants born before 27 weeks' gestation in Sweden. *Archives of Ophthalmology, 127*(10), 1315–1319. doi:10.1001/archophthalmol.2009.244

Aziz, K., & Dancey, P. & Canadian Paediatric Society, Fetus and Newborn Committee. (2004). Screening guidelines for newborns at risk for low blood glucose (Reaffirmed 2018). *Pediatrics and Child Health, 9*(10), 723–729. doi:10.1093/pch/9.10.723

Bain, E., Middleton, P., & Crowther, C. A. (2012). Different magnesium sulphate regimens for neuroprotection of the fetus for women at risk of preterm birth. *The Cochrane Database of Systematic Reviews,* (2), CD009302. doi:10.1002/14651858.CD009302.pub2

Ballot, D. E., Chirwa, T. F., & Cooper, P. A. (2010). Determinants of survival in very low birth weight neonates in a public sector hospital in Johannesburg. *BMC Pediatrics, 10*, 30. doi:10.1186/1471-2431-10-30

Barrington, K. J. (2001). The adverse neuro-developmental effects of postnatal steroids in the preterm infant: A systematic review of RCTs. *BMC Pediatrics*, *1*, 1. doi:10.1186/1471-2431-1-1

Barrington, K. J. (2011). Low blood pressure in extremely preterm infants: Does treatment affect outcome? *Archives of Disease in Childhood—Fetal and Neonatal Edition, 96*(5), F316–F317. doi:10.1136/adc.2010.206599

Bashir, R. A., Thomas, J. P., MacKay, M., Agnew, J., Hubber-Richard, P., Grunau, R. E., & Synnes, A. (2017). Survival, short-term, and long-term morbidities of neonates with birth weight < 500 g. *American Journal of Perinatology, 34*(13), 1333–1339. doi:10.1055/s-0037-1603462

Baud, O., Maury, L., Lebail, F., Ramful, D., El Moussawi, F., Nicaise, C., . . . Alerti, C. (2016). Effect of early low-dose hydrocortisone on survival without bronchopulmonary dysplasia in extremely preterm infants (PREMILOC): A double-blind, placebo-controlled, multicentre, randomised trial. *The Lancet, 387*(10030), 1827–1836. doi:10.1016/S0140-6736(16)00202-6

Baud, O., Trousson, C., Biran, V., Leroy, E., Mohamed, D., & Alberti, C. (2019). Two-year neurodevelopmental outcomes of extremely preterm infants treated with early hydrocortisone: Treatment effect according to gestational age at birth. *Archives of Disease in Childhood—Fetal and Neonatal Edition, 104*, F30–F35. doi:10.1136/archdischild-2017-313756

Beardsall, K., Ogilvy-Stuart, A. L., Ahluwalia, J., Thompson, M., & Dunger, D. B. (2005). The continuous glucose monitoring sensor in neonatal intensive care. *Archives of Disease in Childhood—Fetal and Neonatal Edition, 90*(4), F307–F310. doi:10.1136/adc.2004.051979

Bell, E. F., & Acarregui, M. J. (2008). Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants. *The Cochrane Database of Systematic Reviews,* (1), CD000503. doi:10.1002/14651858.CD000503.pub2

Bell, E. F., Neidich, G. A., Cashore, W. J., & Oh, W. (1979). Combined effect of radiant warmer and phototherapy on insensible water loss in low-birth-weight infants. *The Journal of Pediatrics, 94*(5), 810–813. doi:10.1016/S0022-3476(79)80164-X

Bell, E. F., Warburton, D., Stonestreet, B. S., & Oh, W. (1980). Effect of fluid administration on the development of symptomatic patent ductus arteriosus and congestive heart failure in premature infants. *New England Journal of Medicine, 302*(11), 598–604. doi:10.1056/NEJM198003133021103

Benjamin, D., Stoll, B., Gantz, M., Walsh, M., Sánchez, P., Das, A., Shankaran, S., . . . Goldberg, R. N. (2010). Neonatal candidiasis: Epidemiology, risk factors, and clinical judgment. *Pediatrics, 126*(4), e865–e873. doi:10.1542/peds.2009-3412

Bhatt, D. R., White, R., Martin, G., Van Marter, L. J., Finer, N., Goldsmith, J. P., . . . Ramanathan, R. (2007). Transitional hypothermia in preterm newborns. *Journal of Perinatology, 27*(Suppl. 2), S45–S47. doi:10.1038/sj.jp.7211842

Birnbaum, R., & Limperopoulos, C. (2009). Nonoral feeding practices for infants in the neonatal intensive care unit. *Advances in Neonatal Care, 9*(4), 180–184. doi:10.1097/ANC.0b013e3181aa9c65

Blakely, M., Lally, K., McDonald, S., Brown, R., Barnhart, D., Ricketts, R., . . . Higgins, R. (2005). Postoperative outcomes of extremely low birth-weight infants with necrotizing enterocolitis or isolated intestinal perforation: A prospective cohort study by the NICHD Neonatal Research Network. *Annals of Surgery, 241*(6), 984–989; discussion 989–994. doi:10.1097/01.sla.0000164181.67862.7f

Bombell, S., & McGuire, W. (2009). Early trophic feeding for very low birth weight infants. *The Cochrane Database of Systematic Reviews,* (3), CD000504. doi:10.1002/14651858.CD000504.pub3

Bright, H. R., Babata, K., Allred, E. N., Erdei, C., Kuban, K. C. K., Joseph, R. M., . . . Vogt, K. (2017). Neurocognitive outcomes at 10 years of age in extremely preterm newborns with late-onset bacteremia. *Pediatrics, 187*, 43–49.e1. doi:10.1016/j.jpeds.2017.04.045

Brion, L. P., Bell, E. F., & Raghuveer, T. S. (2003). Vitamin E supplementation for prevention of morbidity and mortality in preterm infants. *The Cochrane Database of Systematic Reviews*, (4), CD003665. doi:10.1002/14651858.CD003665

Brion, L. P., & Campbell, D. E. (2001). Furosemide for symptomatic patent ductus arteriosus in indomethacin-treated infants. *The Cochrane Database of Systematic Reviews*, (3), CD001148. doi:10.1002/14651858.CD001148

Conner, J. M., Soll, R. F., & Edwards, W. H. (2004). Topical ointment for preventing infection in preterm infants. *The Cochrane Database of Systematic Reviews*, (1), CD001150. doi:10.1002/14651858.CD001150.pub2

Cornblath, M., Hawdon, J. M., Williams, A. F., Aynsley-Green, A., Ward-Platt, M. P., Schwartz, R., & Kalhan, S. C. (2000). Controversies regarding definition of neonatal hypoglycemia: Suggested operational thresholds. *Pediatrics, 105*(5), 1141–1145. doi:10.1542/peds.105.5.1141

Corvaglia, L., Rotatori, R., Ferlini, M., Aceti, A., Ancora, G., & Faldella, G. (2007). The effect of body positioning on gastroesophageal reflux in premature infants: Evaluation by combined impedance and pH monitoring. *The Journal of Pediatrics, 151*(6), 591–596, 596.e591. doi:10.1016/j.jpeds.2007.06.014

Costeloe, K. L., Hennessy, E., Gibson, A. T., Marlow, N., & Wilkinson, A. R. (2000). The EPICure study: Outcomes to discharge from hospital for infants born at the threshold of viability. *Pediatrics, 106*(4), 659–671. Retrieved from https://pediatrics.aappublications.org/content/106/4/659

Costeloe, K. L., Hennessy, E. M., Haider, S., Stacey, F., Marlow, N., & Draper, E. S. (2012). Short term outcomes after extreme preterm birth in England: Comparison of two birth cohorts in 1995 and 2006 (the EPICure studies). *British Medical Journal, 345*, e7976. doi:10.1136/bmj.e7976

Cotten, C. M., Taylor, S., Stoll, B., Goldberg, R. N., Hansen, N. I., Sánchez, P. J., . . . Benjamin, D. K., Jr. (2009). Prolonged duration of initial empirical antibiotic treatment is associated with increased rates of necrotizing enterocolitis and death for extremely low birth weight infants. *Pediatrics, 123*(1), 58–66. doi:10.1542/peds.2007-3423

Clyman, R., Wickremasinghe, A., Jhaveri, N., Hassinger, D. C., Attridge, J. T., Sanocka, U., . . . & Couser, R. (2013). Enteral feeding during indomethacin and ibuprofen treatment of a patent ductus arteriosus. *The Journal of Pediatrics, 163*(2), 406–411. doi:10.1016/j.jpeds.2013.01.057

Craft, A. P., Finer, N. N., & Barrington, K. J. (2000). Vancomycin for prophylaxis against sepsis in preterm neonates. *The Cochrane Database of Systematic Reviews*, (2), CD001971. doi:10.1002/14651858.CD001971

Crowther, C. A., McKinlay, C. J., Middleton, P., & Harding, J. E. (2015). Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes. *The Cochrane Database of Systematic Reviews,* (7), CD003935. doi:10.1002/14651858.CD003935.pub4

Cumming, G. G., Hutchinson, A. M., Scott, S. D., Norton, P. G., & Estabrooks, C. A. (2010). The relationship between characteristics of context and research utilization in a pediatric setting. *BMC Health Services Research, 10*, 168. doi:10.1186/1472-6963-10-168

Dalgleish, S. R., Kostecky, L. L., & Blachly, N. (2016). Eating in "SINC": Safe individualized nipple-feeding competence, a quality improvement project to explore infant-driven oral feeding for very premature infants requiring noninvasive respiratory support. *Neonatal Network, 35*(4), 217–227. doi:10.1891/0730-0832.35.4.217

Darlow, B. A., & Graham, P. J. (2011). Vitamin A supplementation to prevent mortality and short- and long-term morbidity in very low birthweight infants. *The Cochrane Database of Systematic Reviews*, (10), CD000501. doi:10.1002/14651858.CD000501.pub3

de Carvalho, M., Torrao, C. T., & Moreira, M. E. (2011). Mist and water condensation inside incubators reduce the efficacy of phototherapy. *Archives of Disease in Childhood—Fetal and Neonatal Edition, 96*(2), F138–F140. doi:10.1136/adc.2010.189423

Denkel, L. A., Schwab, F., Garten, L., Geffers, C., Gastmeier, P., & Piening, B. (2017). Dual-strain probiotics reduce NEC, mortality and neonatal bloodstream infections among extremely low birthweight infants. *Archives of Disease in Childhood—Fetal and Neonatal Edition, 102*(6), F559–F560. doi:10.1136/archdischild-2017-313897

Deshpande, G., Jape, G., Rao, S., & Patole, S. (2017). Benefits of probiotics in preterm neonates in low-income and medium-income countries: A systematic review of randomised controlled trials. *British Medical Journal Open, 7*(12), e017638. doi:10.1136/bmjopen-2017-017638

Dhudasia, M. B., Mukhopadhyay, S., & Puopolo, K. M. (2018). Implementation of the sepsis risk calculator at an academic birth hospital. *Hospital Pediatrics, 8*(5), 243–250. doi:10.1542/hpeds.2017-0180

Dilli, D., Eras, Z., Özkan Ulu, H., Dilmen, U., & Durgut Şakrucu, E. (2012). Does necrotizing enterocolitis affect growth and neurodevelopmental outcome in very low birth weight infants? *Pediatric Surgery International, 28*(5), 471–476. doi:10.1007/s00383-012-3051-4

Dollberg, S., Lusky, A., & Reichman, B. (2005). Patent ductus arteriosus, indomethacin and necrotizing enterocolitis in very low birth weight infants: A population-based study. *Journal of Pediatric Gastroenterology and Nutrition, 40*(2), 184–188.

Doyle, L. W. (2012). Antenatal magnesium sulfate and neuroprotection. *Current Opinions in Pediatrics, 24*(2), 154–159. doi:10.1097/MOP.0b013e3283504da1

Doyle, L. W., Roberts, G., Anderson, P., Callanan, C., Charlton, M., Davey, M.-A., . . . Woods, H. (2011). Changing long-term outcomes for infants 500-999 g birth weight in Victoria, 1979-2005. *Archives of Disease in Childhood—Fetal and Neonatal Edition, 96*(6), F443–F447. doi:10.1136/adc.2010.200576

Ehrenkranz, R. A. (2010). Early nutritional support and outcomes in ELBW infants. *Early Human Development, 86*(Suppl. 1), 21–25. doi:10.1016/j.earlhumdev.2010.01.014

Ehrenkranz, R. A., Dusick, A. M., Vohr, B. R., Wright, L. L., Wrage, L. A., & Poole, W. K. (2006). Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants. *Pediatrics, 117*(4), 1253–1261. doi:10.1542/peds.2005-1368

Eichenwald, E. C., Aina, A., & Stark, A. R. (1997). Apnea frequently persists beyond term gestation in infants delivered at 24 to 28 weeks. *Pediatrics, 100*(3), 354–359. doi:10.1542/peds.100.3.354

El-Mahdy, M. A., Mansoor, F. A., & Jadcherla, S. R. (2017). Pharmacological management of gastroesophageal reflux disease in infants: Current opinions. *Current Opinion in Pharmacology, 37*, 112–117. doi:10.1016/j.coph.2017.10.013

Embleton, N. E., Pang, N., & Cooke, R. J. (2001). Postnatal malnutrition and growth retardation: An inevitable consequence of current recommendations in preterm infants? *Pediatrics, 107*(2), 270–273. doi:10.1542/peds.107.2.270

Englert, J. A., Saunders, R. A., Purohit, D., Hulsey, T. C., & Ebeling, M. (2001). The effect of anemia on retinopathy of prematurity in extremely low birth weight infants. *Journal of Perinatology, 21*(1), 21–26. Retrieved from https://www.nature.com/articles/7200511.pdf

Ewer, A. K., James, M. E., & Tobin, J. M. (1999). Prone and left lateral positioning reduce gastro-oesophageal reflux in preterm infants. *Archives of Disease in Childhood—Fetal and Neonatal Edition, 81*(3), F201–F205. doi:10.1136/fn.81.3.f201

Fanos, V., Antonucci, R., Barberini, L., Noto, A., & Atzori, L. (2012). Clinical application of metabolomics in neonatology. *Journal of Maternal-Fetal and Neonatal Medicine, 25*(Suppl. 1), 104–109. doi:10.3109/14767058.2012.663198

Fanos, V., Pusceddu, M., Dessì, A., & Marcialis, M. A. (2011). Should we definitively abandon prophylaxis for patent ductus arteriosus

in preterm new-borns? *Clinics, 66*(12), 2141–2149. doi:10.1590/s1807-59322011001200022

Feldman, A. G., & Sokol, R. J. (2013). Neonatal cholestasis. *NeoReviews, 14*(2), e63. doi:10.1542/neo.14-2-e63

Fellman, V., Hellström-Westas, L., Norman, M., Westgren, M., Källén, K., Lagercrantz, H., . . . Wennergren, M.; EXPRESS Group. (2009). One-year survival of extremely preterm infants after active perinatal care in Sweden. *Journal of the American Medical Association, 301*(21), 2225–2233. doi:10.1001/jama.2009.771

Fierson, W., Saunders, R. A., Good, W., Palmer, E. A., Phelps, D., Reynolds, J., . . . Ellis, G. S., Jr. (2013). Screening examination of premature infants for retinopathy of prematurity. *Pediatrics, 131*(1), 189–195. doi:10.1542/peds.2012-2996

Finan, E., Campbell, D. M., Aziz, K., & McNamara, P. J. (2017). Update for Canadian NRP providers: A case-based review. *Paediatr Child Health, 22*(6), 351–356. doi:10.1093/pch/pxx095

Fischer, N., Steurer, M., Adams, M., & Berger, T. (2009). Survival rates of extremely preterm infants (gestational age <26 weeks) in Switzerland: Impact of the Swiss guidelines for the care of infants born at the limit of viability. *Archives of Disease in Childhood—Fetal and Neonatal Edition, 94*(6), F407–F413. doi:10.1136/adc.2008.154567

Fogarty, M., Osborn, D. A., Askie, L., Seidler, A. L., Hunter, K., Lui, K., . . . Tarnow-Mordi, W. (2018). Delayed vs early umbilical cord clamping for preterm infants: A systematic review and meta-analysis. *American Journal of Obstetrics and Gynecology, 218*(1), 1–18. doi:10.1016/j.ajog.2017.10.231

Foster, J. P., Seth, R., & Cole, M. J. (2017). Oral immunoglobulin for preventing necrotizing enterocolitis in preterm and low birth weight neonates. *Cochrane Database of Systematic Reviews,* (4). doi: 10.1002/14651858.CD001816.pub2

Fowlie, P. W., Davis, P. G., & McGuire, W. (2010). Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants. *The Cochrane Database of Systematic Reviews*, (7), CD000174. doi:10.1002/14651858.CD000174.pub2

Fuloria, M., Hiatt, D., Dillard, R. G., & O'Shea, T. M. (2000). Gastroesophageal reflux in very low birth weight infants: Association with chronic lung disease and outcomes through 1 year of age. *Journal of Perinatology, 20*(4), 235–239. doi:10.1038/sj.jp.7200352

Gaylord, M. S., Wright, K., Lorch, K., Lorch, V., & Walker, E. (2001). Improved fluid management utilizing humidified incubators in extremely low birth weight infants. *Journal of Perinatology, 21*(7), 438–443. doi:10.1038/sj.jp.7210561

Geary, C., Caskey, M., Fonseca, R., & Malloy, M. (2008). Decreased incidence of bronchopulmonary dysplasia after early management changes, including surfactant and nasal continuous positive airway pressure treatment at delivery, lowered oxygen saturation goals, and early amino acid administration: A historical cohort study. *Pediatrics, 121*(1), 89–96. doi:10.1542/peds.2007-0225

Gilbert, C., Fielder, A., Gordillo, L., Quinn, G., Semiglia, R., Visintin, P., & Zin, A. (2005). Characteristics of infants with severe retinopathy of prematurity in countries with low, moderate, and high levels of development: Implications for screening programs. *Pediatrics, 115*(5), e518–e525. doi:10.1542/peds.2004-1180

Golish, T. D., & Powell, K. A. (2003). "Ambiguous loss": Managing the dialectics of grief associated with premature birth. *Journal of Social and Personal Relationships, 20*(3), 309–334. doi:10.1177/0265407503020003003

Gorski, P. A. (1991). Promoting infant development during neonatal hospitalization: Critiquing the state of the science. *Child Health Care, 20*(4), 250–257. doi:10.1207/s15326888chc2004_9

Grant, L., & Cochran, D. (2001). Can pH monitoring reliably detect gastro-oesophageal reflux in preterm infants? *Archives of Disease in Childhood—Fetal and Neonatal Edition, 85*(3), F155–F157; discussion F157–158. doi:10.1136/fn.85.3.f155

Guillen, U., DeMauro, S., Ma, L., Zupancic, J., Wang, E., Gafni, A., & Kirpalani, H. (2011). Survival rates in extremely low birthweight infants depend on the denominator: Avoiding potential for bias by specifying denominators. *American Journal of Obstetrics and Gynecology, 205*(4), 329.e321-327. doi:10.1016/j.ajog.2011.05.032

Guthrie, S. O., Gordon, P. V., Thomas, V., Thorp, J. A., Peabody, J., & Clark, R. H. (2003). Necrotizing enterocolitis among neonates in the United States. *Journal of Perinatology, 23*(4), 278–285. doi:10.1038/sj.jp.7210892

Håkansson, S., Farooqi, A., Holmgren, P. A., Serenius, F., & Högberg, U. (2004). Proactive management promotes outcome in extremely preterm infants: A population-based comparison of two perinatal management strategies. *Pediatrics, 114*(1), 58–64. doi:10.1542/peds.114.1.58

Hamvas, A. (2011). Part 3: Pathophysiology and management of respiratory distress syndrome. In A. R. J. Martin, A. A. Fanaroff, & M. C. Walsh. (Eds.), *Fanaroff & Martin's neonatal-perinatal medicine* (9th ed., pp. 1106–1115). St. Louis, MO: Mosby.

Haque, K. N., & Pammi, M. (2011). Pentoxifylline for treatment of sepsis and necrotizing enterocolitis in neonates. *The Cochrane Database of Systematic Reviews*, (10), CD004205. doi:10.1002/14651858.CD004205.pub2

Hardy, R., Good, W., Dobson, V., Palmer, E., Phelps, D., Quintos, M., & Tung, B.; (2004). Multicenter trial of early treatment for retinopathy of prematurity: Study design. *Controlled Clinical Trials, 25*(3), 311–325. doi:10.1016/j.cct.2004.03.003

Haward, M. F., Kirshenbaum, N. W., & Campbell, D. E. (2011). Care at the edge of viability: Medical and ethical issues. *Clinics in Perinatology, 38*(3), 471–492. doi:10.1016/j.clp.2011.06.004

Hawdon, J. M., Beauregard, N., Slattery, J., & Kennedy, G. (2000). Identification of neonates at risk of developing feeding problems in infancy. *Developmental Medicine & Child Neurology, 42*(4), 235–239. doi:10.1111/j.1469-8749.2000.tb00078.x

Hays, S. P., Smith, E. O., & Sunehag, A. L. (2006). Hyperglycemia is a risk factor for early death and morbidity in extremely low birth-weight infants. *Pediatrics, 118*(5), 1811–1818. doi:10.1542/peds.2006-0628

Hazan, J., Maag, U., & Chessex, P. (1991). Association between hypothermia and mortality rate of premature infants—Revisited. *American Journal of Obstetrics and Gynecology, 164*(1 Pt 1), 111–112. doi:10.1016/0002-9378(91)90638-8

Helenius, K., Sjörs, G., Shah, P., Modi, N., Reichman, B., Morisaki, N., . . . Lehtonen, L. (2017). Survival in very preterm infants: An international comparison of 10 national neonatal networks. *Pediatrics, 140*(6), e20171264. doi:10.1542/peds.2017-1264

Hellmann, J., Millman, G., & Lodha, A. (2005). Neonatology. In R. M. Laxer (Ed.), *The hospital for sick children atlas of pediatrics* (pp. 52–73). Toronto, ON, Canada: Current Medicine Group.

Henderson-Smart, D. J., & De Paoli, A. G. (2010). Methylxanthine treatment for apnoea in preterm infants. *The Cochrane Database of Systematic Reviews*, (12), CD000140. doi:10.1002/14651858.CD000140.pub2

Henderson-Smart, D. J., & Steer, P. (2004). Doxapram treatment for apnea in preterm infants. *The Cochrane Database of Systematic Reviews*, (4), CD000074. doi:10.1002/14651858.CD000074.pub2

Herrman, K., Bose, C., Lewis, K., & Laughon, M. (2009). Spontaneous closure of the patent ductus arteriosus in very low birth weight infants following discharge from the neonatal unit. *Archives of Disease in Childhood—Fetal and Neonatal Edition, 94*(1), F48–F50. doi:10.1136/adc.2007.129270

Higgins, R. D., Baker, C. J., & Raju, T. N. (2010). Executive summary of the workshop on infection in the high-risk infant. *Journal of Perinatology, 30*(6), 379–383. doi:10.1038/jp.2009.199

Higgins, R. D., Jobe, A. H., Koso-Thomas, M., Bancalari, E., Viscardi, R. M., Hartert, T. V., . . . Raju, T. N. K. (2018). Bronchopulmonary dysplasia: Executive summary of a workshop. *The Journal of Pediatrics, 197*, 300–308. doi:10.1016/j.jpeds.2018.01.043

Hintz, S., Kendrick, D., Wilson-Costello, D., Das, A., Bell, E., Vohr, B., & Higgins, R. D. (2011). Early-childhood neurodevelopmental outcomes are not improving for infants born at <25 weeks' gestational age. *Pediatrics, 127*(1), 62–70. doi:10.1542/peds.2010-1150

Hintz, S., Stevenson, D., Yao, Q., Wong, R., Das, A., Van Meurs, K., . . . Higgins, R. D. (2011). Is phototherapy exposure associated with better or worse outcomes in 501- to 1000-g-birth-weight infants? *Acta Paediatrica, 100*(7), 960–965. doi:10.1111/j.1651-2227.2011.02175.x

Ho, S., & Saigal, S. (2005). Current survival and early outcomes of infants of borderline viability. *NeoReviews, 6*(3), e123–e132. doi:10.1542/neo.6-3-e123

Hodges, C., & Vincent, P. A. (1993). Why do NICU nurses not refeed gastric residuals prior to feeding by gavage? *Neonatal Network, 12*(8), 37–40.

Horbar, J. D., Edwards, E. M., Greenberg, L. T., Morrow, K. A., Soll, R. F., Buus-Frank, M. E., & Buzas, J. S. (2017). Variation in performance of neonatal intensive care units in the United States. *Journal of the American Medical Association Pediatrics, 171*(3), e164396. doi:10.1001/jamapediatrics.2016.4396

Ibrahim, H. M., Jeroudi, M. A., Baier, R. J., Dhanireddy, R., & Krouskop, R. W. (2004). Aggressive early total parental nutrition in low-birth-weight infants. *Journal of Perinatology, 24*(8), 482–486. doi:10.1038/sj.jp.7211114

Ibrahim, H. M., Sinha, I. P., & Subhedar, N. V. (2011). Corticosteroids for treating hypotension in preterm infants. *The Cochrane Database of Systematic Reviews*, (12), CD003662. doi:10.1002/14651858.CD003662.pub4

Iijima, S., Arai, H., Ozawa, Y., Kawase, Y., & Uga, N. (2009). Clinical patterns in extremely preterm (22 to 24 weeks of gestation) infants in relation to survival time and prognosis. *American Journal of Perinatology, 26*(6), 399–406. doi:10.1055/s-0029-1214234

Inoue, H., Ochiai, M., Yasuoka, K., Tanaka, K., Kurata, H., Fujiyoshi, J., . . . Chiga, S. (2017). Early mortality and morbidity in infants with birth weight of 500 grams or less in Japan. *The Journal of Pediatrics, 190*, 112–117.e113. doi:10.1016/j.jpeds.2017.05.017

An international classification of retinopathy of prematurity. (1984). *Pediatrics, 74*(1), 127–133. doi:10.1001/archopht.123.7.991

Isayama, T., Lee, S. K., Yang, J., Lee, D., Daspal, S., Dunn, M., & Shah, P. S. (2017). Revisiting the definition of bronchopulmonary dysplasia: Effect of changing panoply of respiratory support for preterm neonates. *Journal of the American Medical Association Pediatrics, 171*(3), 271–279. doi:10.1001/jamapediatrics.2016.4141

Ishii, N., Kono, Y., Yonemoto, N., Kusuda, S., & Fujimura, M. (2013). Outcomes of infants born at 22 and 23 weeks' gestation. *Pediatrics, 132*(1), 62–71. doi: 10.1542/peds.2012-2857

Janvier, A., Khairy, M., Kokkotis, A., Cormier, C., Messmer, D., & Barrington, K. J. (2004). Apnea is associated with neurodevelopmental impairment in very low birth weight infants. *Journal of Perinatology, 24*(12), 763–768. doi:10.1038/sj.jp.7211182

Jensen, E. A., & Schmidt, B. (2014). Epidemiology of bronchopulmonary dysplasia. *Birth Defects Research Part A: Clinical and Molecular Teratology, 100*(3), 145–157. doi:10.1002/bdra.23235

Johnson, S., Fawke, J., Hennessy, E., Rowell, V., Thomas, S., Wolke, D., & Marlow, N. (2009). Neurodevelopmental disability through 11 years of age in children born before 26 weeks of gestation. *Pediatrics, 124*(2), e249–e257. doi:10.1542/peds.2008-3743

Joshi, N. S., Gupta, A., Allan, J. M., Cohen, R. S., Aby, J. L., Weldon, B., . . . Frymoyer, A. (2018). Clinical monitoring of well-appearing infants born to mothers with chorioamnionitis. *Pediatrics, 141*(4), e20172056. doi:10.1542/peds.2017-2056

Kalhan, S. C., & Devaska, S. U. (2011). Disorders of carbohydrate metabolism. In F. R. J. Martin, A. A. Fanaroff, & M. C. Walsh (Eds.), *Fanaroff & Martin's neonatal-perinatal medicine: Diseases of the fetus and infant* (9th ed., pp. 1497–1522). St. Louis, MO: Mosby.

Kao, L. S., Morris, B. H., Lally, K. P., Stewart, C. D., Huseby, V., & Kennedy, K. A. (2006). Hyperglycemia and morbidity and mortality in extremely low birth weight infants. *Journal of Perinatology, 26*(12), 730–736. doi:10.1038/sj.jp.7211593

Kent, A. L., & Chaudhari, T. (2013). Determinants of neonatal blood pressure. *Current Hypertension Reports, 15*(5), 426–432. doi:10.1007/s11906-013-0375-y

Kilbride, H. W. (2004). Effectiveness of neonatal intensive care for extremely low birth weight infants. *Pediatrics, 114*(5), 1374; author reply 1374–1375. doi:10.1542/peds.2004-1296

Kim, S. M., Lee, E. Y., Chen, J., & Ringer, S. A. (2010). Improved care and growth outcomes by using hybrid humidified incubators in very preterm infants. *Pediatrics, 125*(1), e137–e145. doi:10.1542/peds.2008-2997

Kirpalani, H., Whyte, R. K., Andersen, C., Asztalos, E. V., Heddle, N., Blajchman, M. A., . . . Roberts, R. S. (2006). The premature infants in need of transfusion (PINT) study: A randomized, controlled trial of a restrictive (low) versus liberal (high) transfusion threshold for extremely low birth weight infants. *The Journal of Pediatrics, 149*(3), 301–307.e3. doi:10.1016/j.jpeds.2006.05.011

Kjartansson, S., Hammarlund, K., & Sedin, G. (1992). Insensible water loss from the skin during phototherapy in term and preterm infants. *Acta Paediatrica, 81*(10), 764–768. doi:10.1111/j.1651-2227.1992.tb12099.x

Kliegman, R. M. (1990). Models of the pathogenesis of necrotizing enterocolitis. *The Journal of Pediatrics, 117*(1 Pt 2), S2–S5. doi:10.1016/s0022-3476(05)81123-0

Knobel, R. B., Holditch-Davis, D., Schwartz, T. A., & Wimmer, J. E. (2009). Extremely low birth weight preterm infants lack vasomotor response in relationship to cold body temperatures at birth. *Journal of Perinatology, 29*(12), 814–821. doi:10.1038/jp.2009.99

Knobel, R. B., Wimmer, J. E., & Holbert, D. (2005). Heat loss prevention for preterm infants in the delivery room. *Journal of Perinatology, 25*(5), 304–308. doi:10.1038/sj.jp.7211289

Koch, J., Hensley, G., Roy, L., Brown, S., Ramaciotti, C., & Rosenfeld, C. R. (2006). Prevalence of spontaneous closure of the ductus arteriosus in neonates at a birth weight of 1000 grams or less. *Pediatrics, 117*(4), 1113–1121. doi:10.1542/peds.2005-1528

Kopelman, L. M. (2005). Rejecting the Baby Doe rules and defending a "negative" analysis of the best interests standard. *Journal of Medicine and Philosophy, 30*(4), 331–352. doi:10.1080/03605310591008487

Kotto-Kome, A. C., Garcia, M. G., Calhoun, D. A., & Christensen, R. D. (2004). Effect of beginning recombinant erythropoietin treatment within the first week of life, among very-low-birth-weight neonates, on "early" and "late" erythrocyte transfusions: A meta-analysis. *Journal of Perinatology, 24*(1), 24–29. doi:10.1038/sj.jp.7211018

Kribs, A., & Hummler, H. (2016). Ancillary therapies to enhance success of non-invasive modes of respiratory support—Approaches to delivery room use of surfactant and caffeine? *Seminars in Fetal & Neonatal Medicine, 21*(3), 212–218. doi:10.1016/j.siny.2016.02.011

Kuban, K. C., Allred, E. N., O'Shea, T. M., Paneth, N., Pagano, M., Dammann, O., . . . Keller, C. E. (2009). Cranial ultrasound lesions in the NICU predict cerebral palsy at age 2 years in children born at extremely low gestational age. *Journal of Child Neurology, 24*(1), 63–72. doi:10.1177/0883073808321048

Kuschel, C. A., & Harding, J. E. (2000). Protein supplementation of human milk for promoting growth in preterm infants. *The Cochrane Database of Systematic Reviews*, (2), CD000433. doi:10.1002/14651858.CD000433

Kusuda, S., Fujimura, M., Sakuma, I., Aotani, H., Kabe, K., Itani, Y., . . . Nishida, H. (2006). Morbidity and mortality of infants with very low birth weight in Japan: Center variation. *Pediatrics, 118*(4), e1130–e1138. doi:10.1542/peds.2005-2724

Kyser, K. L., Morriss, F. H., Bell, E. F., Klein, J. M., & Dagle, J. M. (2012). Improving survival of extremely preterm infants born between 22 and 25 weeks of gestation. *Obstetrics & Gynecology, 119*(4), 795–800. doi:10.1097/AOG.0b013e31824b1a03

Labenne, M., Michaut, F., Gouyon, B., Ferdynus, C., & Gouyon, J. B. (2007). A population-based observational study of restrictive guidelines for antibiotic therapy in early-onset neonatal infections. *Pediatric Infectious Disease Journal, 26*(7), 593–599. doi:10.1097/INF.0b013e318068b656

Lee, H. C., Green, C., Hintz, S. R., Tyson, J. E., Parikh, N. A., Langer, J., & Gould, J. B. (2010). Prediction of death for extremely premature infants in a population-based cohort. *Pediatrics, 126*(3), e644–e650. doi:10.1542/peds.2010-0097

Lee, J. S., & Polin, R. A. (2003). Treatment and prevention of necrotizing enterocolitis. *Seminars in Neonatology, 8*(6), 449–459. doi:10.1016/S1084-2756(03)00123-4

Lemyre, B., Davis, P. G., De Paoli, A. G., & Kirpalani, H. (2017). Nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (NCPAP) for preterm neonates

after extubation. *The Cochrane Database of Systematic Reviews*, (2), CD003212. doi:10.1002/14651858.CD003212.pub3

Lemyre, B., Sample, M., Lacaze-Masmonteil, T., & Canadian Paediatric Society, Fetus and Newborn Committee. (2015). Minimizing blood loss and the need for transfusions in very premature infants. *Paediatrics & Child Health, 20*(8), 451–462. doi:10.1093/pch/20.8.451

Lester, B. M., Miller, R. J., Hawes, K., Salisbury, A., Bigsby, R., Sullivan, M. C., & Padbury, J. F. (2011). Infant neurobehavioral development. *Seminars in Perinatology, 35*(1), 8–19. doi:10.1053/j.semperi.2010.10.003

Lightburn, M. H., Gauss, C. H., Williams, D. K., & Kaiser, J. R. (2009). Cerebral blood flow velocities in extremely low birth weight infants with hypotension and infants with normal blood pressure. *The Journal of Pediatrics, 154*(6), 824–828. doi:10.1016/j.jpeds.2009.01.006

Lodha, A., Sauve, R., Bhandari, V., Tang, S., Christianson, H., Bhandari, A., . . . Singhal, N. (2014). Need for supplemental oxygen at discharge in infants with bronchopulmonary dysplasia is not associated with worse neurodevelopmental outcomes at 3 years corrected age. *PLoS One, 9*(3), e90843. doi:10.1371/journal.pone.0090843

Logan, J. W., O'Shea, T. M., Allred, E. N., Laughon, M. M., Bose, C. L., Dammann, O., . . . Leviton, A. (2011). Early postnatal hypotension is not associated with indicators of white matter damage or cerebral palsy in extremely low gestational age newborns. *Journal of Perinatology, 31*(8), 524–534. doi:10.1038/jp.2010.201

Lorenz, J. M. (2003). Management decisions in extremely premature infants. *Seminars in Neonatology, 8*(6), 475–482. doi:10.1016/S1084-2756(03)00118-0

Lorenz, J. M. (2004). Proactive management of extremely premature infants. *Pediatrics, 114*(1), 264. doi:10.1542/peds.114.1.264

Lorenz, J. M., Kleinman, L. I., Ahmed, G., & Markarian, K. (1995). Phases of fluid and electrolyte homeostasis in the extremely low birth weight infant. *Pediatrics, 96*(3 Pt. 1), 484–489. Retrieved from https://pediatrics.aappublications.org/content/96/3/484

Lucas, A., & Cole, T. J. (1990). Breast milk and neonatal necrotising enterocolitis. *The Lancet, 336*(8730), 1519–1523. doi:10.1016/0140-6736(90)93304-8

Lucas, A., Morley, R., Cole, T. J., Lister, G., & Leeson-Payne, C. (1992). Breast milk and subsequent intelligence quotient in children born preterm. *The Lancet, 339*(8788), 261–264. doi:10.1016/0140-6736(92)91329-7

Lyon, A. J., Pikaar, M. E., Badger, P., & McIntosh, N. (1997). Temperature control in very low birthweight infants during first five days of life. *Archives of Disease in Childhood—Fetal and Neonatal Edition, 76*(1), F47–F50. doi:10.1136/fn.76.1.f47

Madan, A., Kumar, R., Adams, M. M., Benitz, W. E., Geaghan, S. M., & Widness, J. A. (2005). Reduction in red blood cell transfusions using a bedside analyzer in extremely low birth weight infants. *Journal of Perinatology, 25*(1), 21–25. doi:10.1038/sj.jp.7211201

Maggio, L., Cota, F., Gallini, F., Lauriola, V., Zecca, C., & Romagnoli, C. (2007). Effects of high versus standard early protein intake on growth of extremely low birth weight infants. *Journal of Pediatric Gastroenterology and Nutrition, 44*(1), 124–129. doi:10.1097/01.mpg.0000237927.00105.f7

Maheshwari, A., Patel, R. M., & Christensen, R. D. (2018). Anemia, red blood cell transfusions, and necrotizing enterocolitis. *Seminars in Pediatric Surgery, 27*(1), 47–51. doi:10.1053/j.sempedsurg.2017.11.009

Maier, R. F., Sonntag, J., Walka, M. M., Liu, G., Metze, B. C., & Obladen, M. (2000). Changing practices of red blood cell transfusions in infants with birth weights less than 1000 g. *The Journal of Pediatrics, 136*(2), 220–224. doi:10.1016/s0022-3476(00)70105-3

Malviya, M., Ohlsson, A., & Shah, S. (2008). Surgical versus medical treatment with cyclooxygenase inhibitors for symptomatic patent ductus arteriosus in preterm infants. *The Cochrane Database of Systematic Reviews*, (1), CD003951. doi:10.1002/14651858.CD003951.pub2

Markestad, T., Kaaresen, P. I., Rønnestad, A., Reigstad, H., Lossius, K., Medbø, S., . . . Irgens, L. M. (2005). Early death, morbidity, and need of treatment among extremely premature infants. *Pediatrics, 115*(5), 1289–1298. doi:10.1542/peds.2004-1482

Marlier, L., Gaugler, C., & Messer, J. (2005). Olfactory stimulation prevents apnea in premature newborns. *Pediatrics, 115*(1), 83–88. doi:10.1542/peds.2004-0865

Martin, R. J., Abu-Shaweesh, J. M., & Baird, T. M. (2004). Apnoea of prematurity. *Paediatric Respiratory Reviews, 5*(Suppl. 1), S377–S382. doi:10.1016/S1526-0542(04)90067-X

Martin, R. J., Fanaroff, A., & Walsh, M. (Eds.). (2015). *Fanaroff & Martin's neonatal-perinatal medicine* (10th ed.). St. Louis, MO: Mosby.

Mazeiras, G., Rozé, J. C., Ancel, P. Y., Caillaux, G., Frondas-Chauty, A., Denizot, S., & Flamant, C. (2012). Hyperbilirubinemia and neurodevelopmental outcome of very low birthweight infants: Results from the LIFT cohort. *PLoS One, 7*(1), e30900. doi:10.1371/journal.pone.0030900

McCain, G. C., Gartside, P. S., Greenberg, J. M., & Lott, J. W. (2001). A feeding protocol for healthy preterm infants that shortens time to oral feeding. *The Journal of Pediatrics, 139*(3), 374–379. doi:10.1067/mpd.2001.117077

McCall, E. M., Alderdice, F., Halliday, H. L., Jenkins, J. G., & Vohra, S. (2010). Interventions to prevent hypothermia at birth in preterm and/or low birthweight infants. *The Cochrane Database of Systematic Reviews*, (3), CD004210. doi:10.1002/14651858.CD004210.pub4

Medoff-Cooper, B., & Ray, W. (1995). Neonatal sucking behaviors. *Image: the Journal of Nursing Scholarship, 27*(3), 195–200. doi:10.1111/j.1547-5069.1995.tb00858.x

Meerstadt, P. W. D., & Gyll, C. (1994). *Manual of neonatal emergency X-ray interpretation*. London, UK: Saunders.

Mehler, K., Grimme, J., Abele, J., Huenseler, C., Roth, B., & Kribs, A. (2012). Outcome of extremely low gestational age newborns after introduction of a revised protocol to assist preterm infants in their transition to extrauterine life. *Acta Paediatrica, 101*(12), 1232–1239. doi:10.1111/apa.12015

Meinzen-Derr, J., Poindexter, B., Wrage, L., Morrow, A. L., Stoll, B., & Donovan, E. F. (2009). Role of human milk in extremely low birth weight infants' risk of necrotizing enterocolitis or death. *Journal of Perinatology, 29*(1), 57–62. doi:10.1038/jp.2008.117

Mercier, C. E., Dunn, M. S., Ferrelli, K. R., Howard, D. B., & Soll, R. F., & Vermont Oxford Network ELBW Infant Follow Up Study Group. (2010). Neurodevelopmental outcome of extremely low birth weight infants from the Vermont Oxford Network: 1998-2003. *Neonatology, 97*(4), 329–338. doi:10.1159/000260136

Meyer, M., Mildenhall, L., & Wong, M. (2004). Outcomes for infants weighing less than 1000 grams cared for with a nasal continuous positive airway pressure-based strategy. *Journal of Paediatrics and Child Health, 40*(1-2), 38–41. doi:10.1111/j.1440-1754.2004.00287.x

Mitchell, K., Lyttle, A., Amin, H., Shaireen, H., Robertson, H. L., & Lodha, A. K. (2014). Arginine supplementation in prevention of necrotizing enterocolitis in the premature infant: An updated systematic review. *BMC Pediatrics, 14*(1), 226. doi:10.1186/1471-2431-14-226

Moll, M., Goelz, R., Naegele, T., Wilke, M., & Poets, C. F. (2011). Are recommended phototherapy thresholds safe enough for extremely low birth weight (ELBW) infants? A report on 2 ELBW infants with kernicterus despite only moderate hyperbilirubinemia. *Neonatology, 99*(2), 90–94. doi:10.1159/000302719

Moore, G. P., Lemyre, B., Barrowman, N., & Daboval, T. (2013). Neurodevelopmental outcomes at 4 to 8 years of children born at 22 to 25 weeks' gestational age: A meta-analysis. *Journal of the American Medical Association Pediatrics, 167*(10), 967–974. doi:10.1001/jamapediatrics.2013.2395

Morgan, J., Young, L., & McGuire, W. (2014). Delayed introduction of progressive enteral feeds to prevent necrotising enterocolitis in very low birth weight infants. *The Cochrane Database of Systematic Reviews*, (12), CD001970. doi:10.1002/14651858.CD001970.pub5

Morris, B. H., Oh, W., Tyson, J. E., Stevenson, D. K., Phelps, D. L., O'Shea, T. M., . . . Higgins, R. D. (2008). Aggressive vs. conservative phototherapy for infants with extremely low birth weight. *New*

England Journal of Medicine, 359(18), 1885–1896. doi:10.1056/NEJMoa0803024

Moya, M. P., Clark, R. H., Nicks, J., & Tanaka, D. T. (2001). The effects of bedside blood gas monitoring on blood loss and ventilator management. *Biology of the Neonate, 80*(4), 257–261. doi:10.1159/000047153

Nakstad, B. (2018). The diagnostic utility of procalcitonin, interleukin-6 and interleukin-8, and hyaluronic acid in the Norwegian consensus definition for early-onset neonatal sepsis (EONS). *Infection and Drug Resistance, 11*, 359–368. doi:10.2147/IDR.S155965

Narendran, V., Donovan, E. F., Hoath, S. B., Akinbi, H. T., Steichen, J. J., & Jobe, A. H. (2003). Early bubble CPAP and outcomes in ELBW preterm infants. *Journal of Perinatology, 23*(3), 195–199. doi:10.1038/sj.jp.7210904

Neu, J., & Walker, W. A. (2011). Necrotizing enterocolitis. *New England Journal of Medicine, 364*(3), 255–264. doi: 10.1056/NEJMra1005408

Ngo, S., Profit, J., Gould, J. B., & Lee, H. C. (2017). Trends in patent ductus arteriosus diagnosis and management for very low birth weight infants. *Pediatrics, 139*(4), e20162390. doi:10.1542/peds.2016-2390

O'Brien, K., Robson, K., Bracht, M., Cruz, M., Lui, K., Alvaro, R., . . . Lee, S. K. (2017). Effectiveness of family integrated care in neonatal intensive care units on infant and parent outcomes: A multicentre, multinational, cluster-randomised controlled trial. *The Lancet, 2*(4), 245–254. doi:10.1016/S2352-4642(18)30039-7

Ohls, R. K. (2002). Erythropoietin treatment in extremely low birth weight infants: Blood in versus blood out. *The Journal of Pediatrics, 141*(1), 3–6. doi:10.1067/mpd.2002.125853

Ohlsson, A., & Shah, S. S. (2011). Ibuprofen for the prevention of patent ductus arteriosus in preterm and/or low birth weight infants. *The Cochrane Database of Systematic Reviews*, (7), CD004213. doi:10.1002/14651858.CD004213.pub3

Ohlsson, A., Walia, R., & Shah, S. S. (2010). Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants. *The Cochrane Database of Systematic Reviews*, (4), CD003481. doi:10.1002/14651858.CD003481.pub4

Omari, T. I. (2009). Apnea-associated reduction in lower esophageal sphincter tone in premature infants. *The Journal of Pediatrics, 154*(3), 374–378. doi:10.1016/j.jpeds.2008.09.009

Omari, T. I., Rommel, N., Staunton, E., Lontis, R., Goodchild, L., Haslam, R. R., . . . Davidson, G. P. (2004). Paradoxical impact of body positioning on gastroesophageal reflux and gastric emptying in the premature neonate. *The Journal of Pediatrics, 145*(2), 194–200. doi:10.1016/j.jpeds.2004.05.026

Osborn, D. A., & Evans, N. (2004). Early volume expansion for prevention of morbidity and mortality in very preterm infants. *The Cochrane Database of Systematic Reviews*, (2), CD002055. doi:10.1002/14651858.CD002055.pub2

Osborn, D. A., & Henderson-Smart, D. J. (2000). Kinesthetic stimulation for treating apnea in preterm infants. *The Cochrane Database of Systematic Reviews*, (2), CD000499. doi:10.1002/14651858.CD000499

O'Shea, T. M., Allred, E. N., Dammann, O., Hirtz, D., Kuban, K. C., Paneth, . . . ELGAN Study Investigators. (2009). The ELGAN study of the brain and related disorders in extremely low gestational age newborns. *Early Human Development, 85*(11), 719–725. doi:10.1016/j.earlhumdev.2009.08.060

Palmer, E. A., Hardy, R. J., Dobson, V., Phelps, D. L., Quinn, G. E., Summers, C. G., . . . Tung, B.; Cryotherapy for Retinopathy of Prematurity Cooperative Group. (2005). 15-year outcomes following threshold retinopathy of prematurity: Final results from the multicenter trial of cryotherapy for retinopathy of prematurity. *Archives of Ophthalmology, 123*(3), 311–318. doi:10.1001/archopht.123.3.311

Pammi, M., & Abrams, S. A. (2011). Oral lactoferrin for the prevention of sepsis and necrotizing enterocolitis in preterm infants. *The Cochrane Database of Systematic Reviews*, (10), CD007137. doi:10.1002/14651858.CD007137.pub3

Pammi, M., & Haque, K. N. (2015). Pentoxifylline for treatment of sepsis and necrotizing enterocolitis in neonates. *The Cochrane Database of Systematic Reviews*, (3), CD004205. doi:10.1002/14651858.CD004205.pub3

Pammi, M., & Suresh, G. (2017). Enteral lactoferrin supplementation for prevention of sepsis and necrotizing enterocolitis in preterm infants. *Cochrane Database of Systematic Reviews*, (6), CD007137. doi:10.1002/14651858.CD007137.pub5.

Patole, S. K., & de Klerk, N. (2005). Impact of standardised feeding regimens on incidence of neonatal necrotising enterocolitis: A systematic review and meta-analysis of observational studies. *Archives of Disease in Childhood—Fetal and Neonatal Edition, 90*(2), F147–F151. doi:10.1136/adc.2004.059741

Penticuff, J. H., & Arheart, K. L. (2005). Effectiveness of an intervention to improve parent-professional collaboration in neonatal intensive care. *Journal of Perinatal and Neonatal Nursing, 19*(2), 187–202. doi:10.1097/00005237-200504000-00016

Peter, C. S., Sprodowski, N., Bohnhorst, B., Silny, J., & Poets, C. F. (2002). Gastroesophageal reflux and apnea of prematurity: No temporal relationship. *Pediatrics, 109*(1), 8–11. doi:10.1542/peds.109.1.8

Peter, C. S., Wiechers, C., Bohnhorst, B., Silny, J., & Poets, C. F. (2002). Influence of nasogastric tubes on gastroesophageal reflux in preterm infants: A multiple intraluminal impedance study. *The Journal of Pediatrics, 141*(2), 277–279. doi:10.1067/mpd.2002.126298

Pfister, R. H., Soll, R., & Wiswell, T. E. (2009). Protein-containing synthetic surfactant versus protein-free synthetic surfactant for the prevention and treatment of respiratory distress syndrome. *The Cochrane Database of Systematic Reviews*, (4), CD006180. doi:10.1002/14651858.CD006180.pub2

Phelps, D. L., & Watts, J. L. (2001). Early light reduction for preventing retinopathy of prematurity in very low birth weight infants. *The Cochrane Database of Systematic Reviews*, (1), CD000122. doi:10.1002/14651858.CD000122

Pickler, R. H., & Reyna, B. A. (2003). A descriptive study of bottle-feeding opportunities in preterm infants. *Advances in Neonatal Care, 3*(3), 139–146. doi:10.1016/s1536-0903(03)00074-2

Poets, C. F., & Brockmann, P. E. (2011). Myth: Gastroesophageal reflux is a pathological entity in the preterm infant. *Seminars in Fetal and Neonatal Medicine, 16*(5), 259–263. doi:10.1016/j.siny.2011.05.001

Poets, C. F., & Lorenz, L. (2018). Prevention of bronchopulmonary dysplasia in extremely low gestational age neonates: Current evidence. *Archives of Disease in Childhood—Fetal and Neonatal Edition, 103*(3), F285–F291. doi:10.1136/archdischild-2017-314264

Poets, C. F., Roberts, R. S., Schmidt, B., Whyte, R. K., Asztalos, E. V., Bader, D., . . . Nelson, H. (2015). Association between intermittent hypoxemia or bradycardia and late death or disability in extremely preterm infants. *Journal of the American Medical Association, 314*(6), 595–603. doi:10.1001/jama.2015.8841

Powell, T. L., Parker, L., Dedrick, C. F., Barrera, C. M., Di Salvo, D., Erdman, F., . . . Saunders, M. (2012). Decisions and dilemmas related to resuscitation of infants born on the verge of viability. *Newborn and Infant Nursing Reviews, 12*(1), 27–32. doi:10.1053/j.nainr.2011.12.004

Premji, S. S. (2005). Standardised feeding regimens: Hope for reducing the risk of necrotising enterocolitis. *Archives of Disease in Childhood—Fetal and Neonatal Edition, 90*(3), F192–F193. doi:10.1136/adc.2004.063198

Premji, S. S., & Chessell, L. (2011). Continuous nasogastric milk feeding versus intermittent bolus milk feeding for premature infants less than 1500 grams. *The Cochrane Database of Systematic Reviews*, (11), CD001819. doi:10.1002/14651858.CD001819.pub2

Premji, S. S., McNeil, D. A., & Scotland, J. (2004). Regional neonatal oral feeding protocol: Changing the ethos of feeding preterm infants. *Journal of Perinatal and Neonatal Nursing, 18*(4), 371–384. doi:10.1097/00005237-200410000-00008

Premji, S. S., Paes, B., Jacobson, K., & Chessell, L. (2002). Evidence-based feeding guidelines for very low-birth-weight infants. *Advances in Neonatal Care, 2*(1), 5–18. doi:10.1053/adnc.2002.31511

Razi, N. M., Humphreys, J., Pandit, P. B., & Stahl, G. E. (1999). Predischarge monitoring of preterm infants. *Pediatric Pulmonology, 27*(2), 113–116. doi:10.1002/(SICI)1099-0496(199902)27:2<113::AID-PPUL7>3.0.CO;2-O

Richards, J., Johnson, A., Fox, G., & Campbell, M. (2009). A second course of ibuprofen is effective in the closure of a clinically significant PDA in ELBW infants. *Pediatrics, 124*(2), e287–e293. doi:10.1542/peds.2008-2232

Rieger-Fackeldey, E., Schaller-Bals, S., & Schulze, A. (2003). Effect of body temperature on the pattern of spontaneous breathing in extremely low birth weight infants supported by proportional assist ventilation. *Pediatric Research, 54*(3), 332–336. doi:10.1203/01.PDR.0000076664.65100.FF

Roberts, D., Brown, J., Medley, N., & Dalziel, S. R. (2017). Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *The Cochrane Database of Systematic Reviews*, (3), CD004454. doi:10.1002/14651858.CD004454.pub3

Rojas-Reyes, M. X., Morley, C. J., & Soll, R. (2012). Prophylactic versus selective use of surfactant in preventing morbidity and mortality in preterm infants. *The Cochrane Database of Systematic Reviews*, (3), CD000510. doi:10.1002/14651858.CD000510.pub2

Rosenfeld, W., Sadhev, S., Brunot, V., Jhaveri, R., Zabaleta, I., & Evans, H. E. (1986). Phototherapy effect on the incidence of patent ductus arteriosus in premature infants: Prevention with chest shielding. *Pediatrics, 78*(1), 10–14. Retrieved from https://pediatrics.aappublications.org/content/78/1/10

Rozé, J. C., & Bréart, G. (2004). Care of very premature infants: Looking to the future. *European Journal of Obstetrics & Gynecology and Reproductive Biology, 117*(Suppl. 1), S29–S32. doi:10.1016/j.ejogrb.2004.07.015

Rysavy, M. A., Li, L., Bell, E. F., Das, A., Hintz, S. R., Stoll, B. J., . . . Higgins, R. D. (2015). Between-hospital variation in treatment and outcomes in extremely preterm infants. *New England Journal of Medicine, 372*(19), 1801–1811. doi:10.1056/NEJMoa1410689

Salhab, W. A., Perlman, J. M., Silver, L., & Sue Broyles, R. (2004). Necrotizing enterocolitis and neurodevelopmental outcome in extremely low birth weight infants <1000 g. *Journal of Perinatology, 24*(9), 534–540. doi:10.1038/sj.jp.7211165

Salvo, V., Lista, G., Lupo, E., Ricotti, A., Zimmermann, L. J. I., Gavilanes, A. W. D., Gitto, E., . . . Gazzolo, D. (2017). Comparison of three non-invasive ventilation strategies (NSIPPV/BiPAP/NCPAP) for RDS in VLBW infants. *Journal of Maternal-Fetal and Neonatal Medicine, 31*(21), 2832–2838. doi:10.1080/14767058.2017.1357693

Sankar, M. J., Sankar, J., & Chandra, P. (2018). Anti-vascular endothelial growth factor (VEGF) drugs for treatment of retinopathy of prematurity. *The Cochrane Database of Systematic Reviews*, (1), CD009734. doi:10.1002/14651858.CD009734.pub3

Sasidharan, P. (1998). Role of corticosteroids in neonatal blood pressure homeostasis. *Clinics in Perinatology, 25*(3), 723–740, xi. doi:10.1016/s0095-5108(18)30108-8

Sauer, P. J., Dane, H. J., & Visser, H. K. (1984). New standards for neutral thermal environment of healthy very low birthweight infants in week one of life. *Archives of Disease in Childhood, 59*(1), 18–22. doi:10.1136/adc.59.1.18

Schanler, R. J. (1995). Suitability of human milk for the low-birthweight infant. *Clinics in Perinatology, 22*(1), 207–222. doi:10.1016/s0095-5108(18)30309-9

Schenk, L. K., & Kelley, J. H. (2010). Mothering an extremely low birth-weight infant: A phenomenological study. *Advances in Neonatal Care, 10*(2), 88–97. doi:10.1097/ANC.0b013e3181d28330

Schlapbach, L. J., Aebischer, M., Adams, M., Natalucci, G., Bonhoeffer, J., Latzin, P., . . . ; Swiss Neonatal Network and Follow Up Group. (2011). Impact of sepsis on neurodevelopmental outcome in a Swiss National Cohort of extremely premature infants. *Pediatrics, 128*(2), e348–e357. doi:10.1542/peds.2010-3338

Schmidt, B., Anderson, P. J., Doyle, L. W., Dewey, D., Grunau, R. E., Asztalos, E. V., . . . Robersts, R. S. (2012). Survival without disability to age 5 years after neonatal caffeine therapy for apnea of prematurity. *Journal of the American Medical Association, 307*(3), 275–282. doi:10.1001/jama.2011.2024

Schmidt, B., Davis, P., Moddemann, D., Ohlsson, A., Roberts, R. S., Saigal, S., . . . Wright, L. L. (2001). Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants. *New England Journal of Medicine, 344*(26), 1966–1972. doi:10.1056/NEJM200106283442602

Schmidt, B., Roberts, R. S., Davis, P., Doyle, L. W., Barrington, K. J., Ohlsson, A., . . . Tin, W. (2007). Long-term effects of caffeine therapy for apnea of prematurity. *New England Journal of Medicine, 357*(19), 1893–1902. doi:10.1056/NEJMoa073679

Schoonakker, B., & Smith, C. (2007). How do neonatologists approach early treatment decisions at the extremes of prematurity? *Obstetrics, Gynaecology & Reproductive Medicine, 17*(8), 249–251. doi:10.1016/j.ogrm.2007.06.006

Sehgal, A. (2011). Haemodynamically unstable preterm infant: An unresolved management conundrum. *European Journal of Pediatrics, 170*(10), 1237–1245. doi:10.1007/s00431-011-1435-4

Seri, I., & Evans, J. (2008). Limits of viability: Definition of the gray zone. *Journal of Perinatology, 28*(Suppl. 1), S4–S8. doi:10.1038/jp.2008.42

Shaker, C. S. (1990). Nipple feeding premature infants: A different perspective. *Neonatal Network, 8*(5), 9–17.

Silverman, W. (1992). Foreword. In J. C. Sinclair & M. B. Bracken (Eds.), *Effective care of the newborn*. New York, NY: Oxford University Press.

Sinclair, J. C., Bottino, M., & Cowett, R. M. (2011). Interventions for prevention of neonatal hyperglycemia in very low birth weight infants. *The Cochrane Database of Systematic Reviews*, (10), CD007615. doi:10.1002/14651858.CD007615.pub3

Sinclair, L., & Sinn, J. K. (2009). Higher versus lower humidity for the prevention of morbidity and mortality in preterm infants in incubators (Protocol). *The Cochrane Database of Systematic Reviews*, (2), CD006472. doi:10.1002/14651858.CD006472

Skelton, R., Evans, N., & Smythe, J. (1994). A blinded comparison of clinical and echocardiographic evaluation of the preterm infant for patent ductus arteriosus. *Journal of Paediatrics and Child Health, 30*(5), 406–411. doi:10.1111/j.1440-1754.1994.tb00689.x

Smith, L. (2005). The ethics of neonatal care for the extremely preterm infant. *The Journal of Neonatal Nursing, 11*(1), 40–58. doi:10.1016/j.jnn.2005.04.007

Soraisham, A. S., Amin, H. J., Al-Hindi, M. Y., Singhal, N., & Sauve, R. S. (2006). Does necrotising enterocolitis impact the neurodevelopmental and growth outcomes in preterm infants with birthweight ≤ 1250 g? *Journal of Paediatrics and Child Health, 42*(9), 499–504. doi:10.1111/j.1440-1754.2006.00910.x

Spitzer, A. R. (2012). Evidence-based methylxanthine use in the NICU. *Clinics in Perinatology, 39*(1), 137–148. doi:10.1016/j.clp.2011.12.011

Stark, A. R., Carlo, W. A., Tyson, J. E., Papile, L.-A., Wright, L. L., Shankaran, S., . . . Stevenson, D. K. (2001). Adverse effects of early dexamethasone treatment in extremely-low-birth-weight infants. *New England Journal of Medicine, 344*(2), 95–101. doi:10.1056/NEJM200101113440203

Stephens, B. E., Walden, R. V., Gargus, R. A., Tucker, R., McKinley, L., Mance, M., . . . Vohr, B. R. (2009). First-week protein and energy intakes are associated with 18-month developmental outcomes in extremely low birth weight infants. *Pediatrics, 123*(5), 1337–1343. doi:10.1542/peds.2008-0211

Stokowski, L. A. (2005). A primer on apnea of prematurity. *Advances in Neonatal Care, 5*(3), 155–170; quiz 171–154. doi:10.1016/j.adnc.2005.02.010

Stoll, B. J., Hansen, N. I., Adams-Chapman, I., Fanaroff, A. A., Hintz, S. R., Vohr, B., & Higgins, R. D. (2004). Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. *Journal of the American Medical Association, 292*(19), 2357–2365. doi:10.1001/jama.292.19.2357

Stoll, B. J., Hansen, N. I., Bell, E. F., Shankaran, S., Laptook, A. R., Walsh, M. C., . . . Higgins, R. D. (2010). Neonatal outcomes of extremely

preterm infants from the NICHD neonatal research network. *Pediatrics, 126*(3), 443–456. doi:10.1542/peds.2009-2959

Stoll, B. J., Hansen, N. I., Bell, E. F., Walsh, M. C., Carlo, W. A., Shankaran, S., . . . Higgins, R. D. (2015). Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993–2012. *Journal of the American Medical Association, 314*(10), 1039–1051. doi:10.1001/jama.2015.10244

Straus, S. E., Graham, I. D., & Mazmanian, P. E. (2006). Knowledge translation: Resolving the confusion. *Journal of Continuing Education in the Health Professions, 26*(1), 3–4. doi:10.1002/chp.45

Subhani, M., Combs, A., Weber, P., Gerontis, C., & DeCristofaro, J. D. (2001). Screening guidelines for retinopathy of prematurity: The need for revision in extremely low birth weight infants. *Pediatrics, 107*(4), 656–659. doi:10.1542/peds.107.4.656

Subhedar, N. V., & Shaw, N. J. (2003). Dopamine versus dobutamine for hypotensive preterm infants. *The Cochrane Database of Systematic Reviews*, (3), CD001242. doi:10.1002/14651858.CD001242

Sullivan, S., Schanler, R. J., Kim, J. H., Patel, A. L., Trawöger, R., Kiechl-Kohlendorfer, U., . . . Lucas, A. (2010). An exclusively human milk-based diet is associated with a lower rate of necrotizing enterocolitis than a diet of human milk and bovine milk-based products. *The Journal of Pediatrics, 156*(4), 562–567.e561. doi:10.1016/j.jpeds.2009.10.040

Sydnor-Greenberg, N., & Dokken, D. (2000). Coping and caring in different ways: Understanding and meaningful involvement. *Pediatric Nursing, 26*(2), 185–190.

Symington, A., & Pinelli, J. (2006). Developmental care for promoting development and preventing morbidity in preterm infants. *The Cochrane Database of Systematic Reviews*, (2), CD001814. doi:10.1002/14651858.CD001814.pub2

Taylor, J. E., Hawley, G., Flenady, V., & Woodgate, P. G. (2011). Tracheal suctioning without disconnection in intubated ventilated neonates. *The Cochrane Database of Systematic Reviews*, (12), CD003065. doi:10.1002/14651858.CD003065.pub2

Tolsma, K. W., Allred, E. N., Chen, M. L., Duker, J., Leviton, A., & Dammann, O. (2011). Neonatal bacteremia and retinopathy of prematurity: The ELGAN study. *Archives of Ophthalmology, 129*(12), 1555–1563. doi:10.1001/archophthalmol.2011.319

Tomlinson, M. W., Kaempf, J. W., Ferguson, L. A., & Stewart, V. T. (2010). Caring for the pregnant woman presenting at periviable gestation: Acknowledging the ambiguity and uncertainty. *American Journal of Obstetrics and Gynecology, 202*(6), 529.e521-526. doi:10.1016/j.ajog.2009.10.858

Tyson, J. E., Parikh, N. A., Langer, J., Green, C., & Higgins, R. D. (2008). Intensive care for extreme prematurity—Moving beyond gestational age. *New England Journal of Medicine, 358*(16), 1672–1681. doi:10.1056/NEJMoa073059

Uauy, R., & Mena, P. (2001). Lipids and neurodevelopment. *Nutrition Reviews, 59*(8), S34–S48. doi:10.1111/j.1753-4887.2001.tb05500.x

Vanhaesebrouck, P., Allegaert, K., Bottu, J., Debauche, C., Devlieger, H., Docx, M., . . . Van Reempts, P. (2004). The EPIBEL study: Outcomes to discharge from hospital for extremely preterm infants in Belgium. *Pediatrics, 114*(3), 663–675. doi:10.1542/peds.2003-0903-L

Van Overmeire, B., Allegaert, K., Casaer, A., Debauche, C., Decaluwé, W., Jespers, A., . . . Langhendries, J. P. (2004). Prophylactic ibuprofen in premature infants: A multicentre, randomised, double-blind, placebo-controlled trial. *The Lancet, 364*(9449), 1945–1949. doi:10.1016/S0140-6736(04)17477-1

Venkataraman, R., Kamaludeen, M., Amin, H., & Lodha, A. (2018). Is less noise, light and parental/caregiver stress in the neonatal intensive care unit better for neonates? *Indian Pediatrics, 55*(1), 17–21. doi:10.1007/s13312-018-1220-9

Vohr, B. R., Poindexter, B. B., Dusick, A. M., McKinley, L. T., Wright, L. L., Langer, J. C., & Poole, W. K. (2006). Beneficial effects of breast milk in the neonatal intensive care unit on the developmental outcome of extremely low birth weight infants at 18 months of age. *Pediatrics, 118*(1), e115–e123. doi:10.1542/peds.2005-2382

Vohr, B. R., Wright, L. L., Dusick, A. M., Perritt, R., Poole, W. K., Tyson, J. E., . . . Mayes, L. C. (2004). Center differences and outcomes of extremely low birth weight infants. *Pediatrics, 113*(4), 781–789. doi:10.1542/peds.113.4.781

Walsh, M. C., Kliegman, R. M. (1986). Necrotizing enterocolitis: treatment based on staging criteria. *Pediatric Clinics of North America, 33*(1), 179–201.

Weiner, G. M., & Zaichkin, J. (Eds.). (2016). *The textbook of neonatal resuscitation* (7th ed.). Itasca, IL: American Academy of Pediatrics.

Whyte, R., & Kirpalani, H. (2011). Low versus high haemoglobin concentration threshold for blood transfusion for preventing morbidity and mortality in very low birth weight infants. *The Cochrane Database of Systematic Reviews,* (11), CD000512. doi:10.1002/14651858.CD000512.pub2

Whyte, R. K., Kirpalani, H., Asztalos, E. V., Andersen, C., Blajchman, M., Heddle, N., . . . Roberts, R. S. (2009). Neurodevelopmental outcome of extremely low birth weight infants randomly assigned to restrictive or liberal hemoglobin thresholds for blood transfusion. *Pediatrics, 123*(1), 207–213. doi:10.1542/peds.2008-0338

Wilder, M. A. (2000). Ethical issues in the delivery room: Resuscitation of extremely low birth weight infants. *Journal of Perinatal & Neonatal Nursing, 14*(2), 44–57. doi:10.1097/00005237-200009000-00006

Wood, N. S., Costeloe, K., Gibson, A. T., Hennessy, E. M., Marlow, N., & Wilkinson, A. R. (2003). The EPICure study: Growth and associated problems in children born at 25 weeks of gestational age or less. *Archives of Disease in Childhood—Fetal and Neonatal Edition, 88*(6), F492–F500. doi:10.1136/fn.88.6.f492

Wood, N. S., Marlow, N., Costeloe, K., Gibson, A. T., & Wilkinson, A. R.(2000). Neurologic and developmental disability after extremely preterm birth. EPICure study group. *New England Journal of Medicine, 343*(6), 378–384. doi:10.1056/NEJM200008103430601

Wyllie, J. (2003). Treatment of patent ductus arteriosus. *Seminars in Neonatology, 8*(6), 425–432. doi:10.1016/S1084-2756(03)00121-0

Yeo, K. L., Perlman, M., Hao, Y., & Mullaney, P. (1998). Outcomes of extremely premature infants related to their peak serum bilirubin concentrations and exposure to phototherapy. *Pediatrics, 102*(6), 1426–1431. doi:10.1542/peds.102.6.1426

Younge, N., Goldstein, R. F., Bann, C. M., Hintz, S. R., Patel, R. M., Smith, P. B., . . . Cotten, C. M. (2017). Survival and neurodevelopmental outcomes among periviable infants. *New England Journal of Medicine, 376*(7), 617–628. doi:10.1056/NEJMoa1605566

Ziegler, E. E., Thureen, P. J., & Carlson, S. J. (2002). Aggressive nutrition of the very low birthweight infant. *Clinics in Perinatology, 29*(2), 225–244. doi:10.1016/S0095-5108(02)00007-6

Zubrow, A. B., Hulman, S., Kushner, H., & Falkner, B. (1995). Determinants of blood pressure in infants admitted to neonatal intensive care units: A prospective multicenter study. Philadelphia neonatal blood pressure study group. *Journal of Perinatology, 15*(6), 470–479.

CHAPTER 29

The Late Preterm Infant

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INTRODUCTION

Late preterm infants are infants born between 34-0/7 and 36-6/7 weeks, and are of increasing interest to medical providers caring for them throughout the country and around the world. In 2011, preterm births affected approximately 11.7% of all births with 71% being late preterm infants (Ramachandrappa & Jain, 2015).

There are two main etiologic categories of late preterm births, spontaneous late preterm births and babies born after induction of labor or cesarean section. Spontaneous late preterm births result from complications of preterm labor and premature rupture of membranes. Inductions of labor or cesarean sections are indicated for many fetal and maternal factors including maternal medical conditions, advanced maternal age, assisted reproductive techniques, multiple births, planned cesarean sections, and maternal request (Mohan & Jain, 2011).

Late preterm infants are larger in size than most premature infants, but they are proving to have many challenges associated with immaturity and delayed transition. These infants have higher rates of morbidity and mortality, as well as increased medical complications, neonatal intensive care unit (NICU) admissions, and prolonged hospitalization (Raju, 2017; Ramachandrappa & Jain, 2015). Late preterm infants require closer monitoring and specialized medical and nursing care for this higher risk population with stricter discharge criteria and follow-up care. These infants have a higher rehospitalization rate and long-term sequelae. Additional research is needed to gain a better understanding of late preterm infants. This knowledge will help to guide obstetrical and neonatal care to reduce the late preterm infant birth rate and provide specialized care to improve patient outcomes in the future (Raju, 2017; Ramachandrappa & Jain, 2015).

DEFINITION

Since 1950, the definition for premature infants has been infants born before 37 completed weeks' gestation (259th day), counting from the first day of the last menstrual period. This definition was established by the World Health Organization (WHO), and the American Academy of Pediatrics (AAP) and American Congress of Obstetricians and Gynecologists (ACOG) concur (Raju, Higgins, Stark, & Leveno, 2006). Within the premature infant category, there are subgroups with definitions including extremely preterm infants (infants <28 weeks' gestation) and very preterm infants (infants <32 weeks' gestation). However, there is less clarity regarding infants born between 32 and 37 weeks' gestation. In July 2005, the National Institute of Child Health and Human Development (NICHD) of the National Institutes of Health (NIH) defined late preterm infants as infants born between 34 0/7 and 36 6/7 weeks (Raju et al., 2006). In developing this definition, many factors were taken into account, especially 34 weeks' gestation being a maturational milestone in which surfactant is usually present. Labeling infants born between 34 0/7 and 36 6/7 weeks late preterm infants was critical in reminding caregivers that these infants are still premature and can develop physical and neurocognitive sequelae and will help discourage early elective deliveries and encourage specialized care optimizing outcomes (Horgan, 2015; Raju, 2017; Ramachandrappa & Jain, 2015; Shapiro-Mendoza & Lackritz, 2012).

INCIDENCE AND EPIDEMIOLOGY

There had been an increase in the preterm birth rate between 1981 and 2006 of 33% that has almost entirely been due to late preterm infant births. In 2008, 12.5% of all births in the United States were infants less than 37 weeks. Of these infants, 72% were late preterm infants born between 34 and 36 weeks. Vital statistics from 2013 to 2014 showed preterm birth rates declined for seven straight years; in 2014 they reached 9.57%, with the low birth weight unchanged at 8% (Murphy, Mathews, Martin, Minkovitz, & Strobino, 2017; Shapiro-Mendoza & Lackritz, 2012). However, for the last two years, premature birth rates in the United States have risen with late preterm infants contributing the largest part of this rise to 9.8% in 2017 (March of Dimes, 2017).

Of these late preterm births, multiple gestations have an elevated birth rate compared with singletons and triplet births as well as higher order birth rates that are decreased in 2014. Overall, between 2013 and 2014, the infant mortality rate decreased by 2.3%, the neonatal mortality rate decreased by 2.5%, and the perinatal mortality rate did not significantly change (Murphy et al., 2017; Shapiro-Mendoza & Lackritz, 2012).

ETIOLOGIC FACTORS CAUSING LATE PRETERM INFANT BIRTHS

The etiologic factors contributing to late preterm births are complex and multifactorial. There are two main categories leading to late preterm births: spontaneous late preterm births and induction of labor or cesarean section for maternal or fetal indications (Gyamfi-Bannerman, 2012; Mohan & Jain, 2011).

The first category, spontaneous late preterm births, relates to conditions where prevention of delivery is typically unavoidable. Maternal risk factors include preterm labor and premature rupture of membranes. This is especially prevalent when infection and inflammation are a concern. Research in the area of expeditious deliveries with preterm labor or PPROM versus expectant management to 37 weeks' gestation is ongoing (Gyamfi-Bannerman, 2012; Mohan & Jain, 2011). The second category includes late preterm births related to inductions of labor and cesarean sections for maternal or fetal indications. The indications for delivery in this group include preeclampsia, eclampsia, intrauterine growth restriction (IUGR), and planned cesarean sections. There has been a dramatic increase in cesarean sections due to increased fetal surveillance and interventions, increasing age of women giving birth, increase in multiple births due to fertility treatments, and heightened concerns of physicians and mothers regarding risks of vaginal births (Mohan & Jain, 2011).

Other factors that impact late preterm births include maternal medical conditions, advanced maternal age, assisted reproductive technologies, and multiple births, which are all associated with preterm births. Gestational age assessments and obstetric practice guidelines can also impact late preterm births. Inaccurate gestational age assessment during elective deliveries can lead to late preterm deliveries, especially with maternal obesity and gestational diabetes. In 2012, the ACOG recommended avoidance of nonmedically indicated early-term deliveries before 39 weeks. There was a decrease in late preterm births from 2006 to 2014 (Raju, 2017). Vink and Gyamfi-Bannerman (2017) have dedicated a two-part series in Seminars of Perinatology to use a diverse group of experts to provide the most up-to-date information from cutting edge research to decrease preterm births.

Decisions regarding obstetric intervention lie with risks and benefits of continuing the pregnancy versus early delivery. Understanding the risks of a suboptimal uterine environment and the risks of late preterm infants is critical to help guide optimal clinical decision making. Further research in this area is necessary to guide clinical practice (Shapiro-Mendoza & Lackritz, 2012).

PATHOPHYSIOLOGIC IMMATURITY OF THE LATE PRETERM INFANT

Late preterm infants can be deceiving: They appear to be larger and mature, but are in fact physiologically and metabolically immature. Their immature systems can predispose them to medical complications, with increased morbidity and mortality rates. A systematic review of their potential immature systems follows.

Respiratory System

Late preterm infants are at higher risk for an immature respiratory system. These infants are at risk for an immature lung structure associated with the interruption of the transition from alveoli lined with cuboidal type II and flat type I epithelial cells (terminal sac period) to mature alveoli lined with thin type I epithelial cells (alveolar period). This can be associated with delayed intrapulmonary fluid absorption, surfactant deficiency and insufficiency, as well as inefficient gas exchange. Late preterm infants are often delivered by cesarean section that occurs without the benefit of labor. Without labor, adrenergic and steroid hormones are not released, leading to a deficit in surfactant production and release. This leaves the late preterm infant at risk for respiratory disorders including transient tachypnea of the newborn (TTN), respiratory distress syndrome (RDS), persistent pulmonary hypertension of the newborn (PPHN), and respiratory failure (Ramachandrappa & Jain, 2015).

The late preterm infant can also have an increased risk of hypoxic respiratory depression, decreased central chemosensitivity to carbon dioxide, immature pulmonary irritant receptors, increased respiratory inhibition sensitivity to laryngeal stimulation, as well as decreased upper airway dilator muscle tone that can leave them at risk for apnea. Apnea in this group can also be due to centrally mediated apnea related to central nervous system immaturity (Ramachandrappa & Jain, 2015).

Cardiac System

There is less understanding of the cardiac pathophysiology in the late preterm infant. It appears these infants are at risk for cardiovascular structure and function immaturities, leading to decreased cardiac reserve during times of stress. There can also be delayed ductal arteriosus closure and persistent pulmonary hypertension, which can complicate their recovery from respiratory disorders (Ramachandrappa & Jain, 2015).

Metabolic System

Immaturities can leave the late preterm infants with decreased stores of brown-fat adipose and white adipose tissue, insufficient concentrations of hormones responsible for brown-fat metabolism, and a decreased surface area to body weight. This leads to an inability to generate heat combined with an increased loss of heat, leading to thermoregulation issues with resultant hypothermia (Ramachandrappa & Jain, 2015).

Late preterm infants have a decreased activity of hepatic uridine diphosphoglucuronate glycuronosyltransferase enzyme, which typically binds bilirubin to glucuronic acid, making it more soluble and more easily secreted in the stool and urine. These infants have a decreased stool frequency and are often dehydrated with a low urine output, making bilirubin excretion difficult. They also have an increased enterohepatic circulation related to immature gastrointestinal function and motility, with a decreased ability for hepatic uptake and conjugation of bilirubin. These factors leave late preterm infants at risk for elevated serum bilirubin levels, with resultant hyperbilirubinemia (Ramachandrappa & Jain, 2015).

Late preterm infants also have an immature hepatic glycogenolysis and adipose tissue lipolysis, as well as hormone dysregulation and less hepatic glyconeogenesis and ketogenesis. This leaves them less able to respond to the abrupt loss of maternal glucose after birth with resultant hypoglycemia (Ramachandrappa & Jain, 2015).

Gastrointestinal System

Immature feeding patterns are a common occurrence when introducing enteral feeds in the late preterm infant. This is related to low oral motor tone with lower intraoral pressure during sucking and neuronal immaturity with resultant poor coordination of suck and swallow patterns (Ramachandrappa & Jain, 2015). These infants also have decreased peristalsis and sphincter control in the esophagus, stomach, and intestines. These immaturities lead to a compromised nutritional status (Ramachandrappa & Jain, 2015).

Central Nervous System

Late premature infants are at risk for neurologic immaturity, with brain weights of only 65% and cerebral volume 53% compared with term infants. These infants have a cerebral cortex that is still smooth, gyri and sulci that are not fully formed, and incomplete myelination and interneural connections. If injury occurs during this neurologic growth period, the infant is at risk for white and gray matter injury, especially in the thalamic region and periventricular white matter. This leaves the late preterm infant at risk for neurologic disorders including poor development and long-term outcome (Ramachandrappa & Jain, 2015).

MORBIDITY AND MORTALITY OF THE LATE PRETERM INFANT

Late preterm infants are at increased risk for morbidity and mortality (Horgan, 2015; King, Gazmarian, & Shapiro-Mendoza, 2014). Cheng, Kaimal, Bruckner, Halloran, and Caughey (2011) researched singleton live births between 34 and 40 weeks of gestation. Infants at 34 weeks were found to be at greatest risk for hyaline membrane disease, mechanical ventilation use greater than 6 hours, and antibiotic use. At 35 weeks, infants had a greater use of surfactant, ventilation greater than 6 hours, and NICU admission. Infants at 36 weeks had an overall higher risk of morbidities when compared to infants 37 to 40 weeks of gestation. The researchers concluded that although the risk of neonatal complications decreased with increasing gestational age, neonatal complications are higher for late preterm infants than their term infant counterparts.

The morbidities that the late preterm infants are at increased risk for include TTN, RDS, PPHN, respiratory failure, apnea, hyperbilirubinemia, hypoglycemia, hypothermia, feeding difficulties, and neonatal sepsis. These health issues place the infants at increased risk for admission to the NICU, requiring treatments including mechanical ventilation, intravenous fluids, and sepsis evaluation (Horgan 2015; Mally, Hendricks-Munos, & Baily, 2013).

Preterm infants also have higher mortality rates. King et al. (2014) found that infant mortality rates for late preterm infants were three times higher than for infants born at 39 to 41 weeks. **Quality and Safety:** **The three leading causes of infant mortality in all infants studied were congenital malformations, sudden infant death, and accidents (unintentional injury).** Crump, Sundquist, Sundquist, and Winkleby (2011) found late preterm infants had a higher mortality rate when compared with term infants during early childhood and young adulthood. Causes of death in young adulthood were related to congenital anomalies, as well as respiratory, endocrine, and cardiovascular disorders.

MEDICAL AND NURSING CARE OF THE LATE PRETERM INFANT

It is clear that late preterm infants are different from term infants and should be monitored more closely. Infants born less than 35 weeks' gestation or less than 2,300 g birth weight should be admitted to an area where they can be observed more closely than in the normal nursery. These infants are at increased risk for delayed transition. These infants should have a physical examination and accurate gestational age assessment on admission. Vital signs and pulse oximeter checks should be done on admission, every 3 to 4 hours in the first 24 hours, and every other shift thereafter. Strong feeding plans should be developed with a formal breastfeeding evaluation done by a trained lactation consultant or neonatal nurse. Serum glucose monitoring should be done to assess for hypoglycemia. Transfer to normal nursery or mother's room should be considered only when the late preterm infant shows signs of stability. If an oxygen hood is needed in excess of 40%, the infant should be transferred to a NICU or tertiary care facility for further management (Horgan, 2015; Phillips et al., 2013; Ramachandrappa & Jain, 2015).

Late preterm infants are at increased risk for TTN, RDS, PPHN, respiratory failure, apnea, hyperbilirubinemia, hypothermia, hypoglycemia, feeding difficulties, neonatal sepsis, and NICU admission with a prolonged hospital stay as well as having mothers with increased emotional distress. These medical problems need careful assessment and treatment (Mally et al., 2013; Phillips et al., 2013; Ramachandrappa & Jain, 2015).

Respiratory Disorders

Late preterm infants are at increased risk for respiratory complications. They include TTN, RDS, PPHN, respiratory failure, and apnea (Horgan, 2015; Mally et al., 2013; Montenegro et al., 2017).

Researchers have found the incidence of RDS was 3% at 36 weeks' gestation, 4% at 35 weeks' gestation, and 9% at 34 weeks' gestation compared to term 40-week infants of 0%. Late preterm infants have an increased need for mechanical ventilation and surfactant replacement, as well as continuous positive airway pressure compared to term infants (Mally et al., 2013; Ramachandrappa & Jain, 2015). **Emergency Alert:** **Late preterm infants should be observed for respiratory symptoms including tachypnea, retractions, nasal flaring, grunting, and cyanosis.** Babies should be admitted to the NICU if respiratory disorders are suspected for monitoring, oxygen therapy, intubation, and surfactant as needed (Ramachandrappa & Jain, 2015).

Late preterm infants are at higher risk for apnea (Horgan, 2015; Mally et al., 2013). Infants should be monitored for apnea and transferred to the NICU for an appropriate workup and treatment as needed. It is important to rule out other causes of apnea such as sepsis. If central apnea is suspected, treatment options include monitoring of apneic events in mild cases and the use of caffeine for more persistent episodes of apnea (Horgan, 2015; Ramachandrappa & Jain, 2015). Researchers in Boston found outpatient management was a cost-effective option for late preterm infants with persistent apnea of prematurity controlled with caffeine and on home monitoring (Montenegro et al., 2017).

Hyperbilirubinemia

Late preterm infants are at risk for hyperbilirubinemia due to an increased bilirubin load and decreased bilirubin excretion. Late preterm infants are also at increased risk of developing kernicterus since many infants are breastfeeding with inadequate maternal supports and insufficient follow-up. These infants should be observed for jaundice as well as have a risk assessment plan for jaundice. A predischarge bilirubin check should be done (serum or transcutaneous) with phototherapy as needed. Careful follow-up should be done to assess for jaundice since bilirubin levels are likely to peak at day 5 to 7 (Horgan, 2015; Ramachandrappa & Jain, 2015).

Hypoglycemia

Late preterm infants are at greater risk for hypoglycemia. It is important to prevent hypoglycemia because even moderate hypoglycemia can have serious neurodevelopmental consequences in the late preterm infants. **Quality and Safety:** **These infants should have their blood sugars monitored frequently, every hour for 4 hours or until greater than 50 twice. Late preterm infants should be monitored for symptoms of hypoglycemia including poor feeding, hypothermia, crying, irritability, jitteriness, seizures, and apnea.**

Treatment will be necessary for a glucose level less than 40 to 50. These treatments include early enteral feeds, intravenous dextrose (2 mL/kg) bolus or maintenance IV fluids (GIR 4–6 mg/kg/minute, Total Fluids 80 mL/kg/day), or a combination of these therapies (Horgan, 2015; Ramachandrappa & Jain, 2015).

Infants of diabetic mothers are often delivered early and will be at greater risk for hypoglycemia. Most institutions have glucose monitoring and protocols that should be followed as needed.

Hypothermia

Thermoregulation is a challenge for the late preterm infant. **Quality and Safety: Late preterm infants' temperatures should be monitored closely after birth, every hour for 6 hours, and then every 6 hours until discharge.** The normal range is 36.5°C to 37.4°C (97.7°F–99.3°F; Horgan, 2015; Ramachandrappa & Jain, 2015).

Infants should be monitored for cold stress symptoms including tachypnea, poor color, cyanosis, pallor, mottling, altered pulmonary vasomotor tone, metabolic acidosis, and lethargy. Hypothermia can worsen respiratory transition and hypoglycemia. **Emergency Alert: These symptoms combined with hypothermia can also suggest infection. Therefore, it is important to prevent these symptoms and an unnecessary costly workup for sepsis** (Ramachandrappa & Jain, 2015).

It is important to keep the infant normothermic using strategies including skin-to-skin contact with the mother, keeping a dry hat on the infant, and using warm blankets in the delivery room. It is also important to keep the infant warm when weighing and postponing a bath until stable (Horgan, 2015; Ramachandrappa & Jain, 2015).

Feeding Difficulties

The gastrointestinal tract of late preterm infants typically tolerates feedings, but these infants often have difficulty in coordination while sucking, swallowing, and breathing. Poor feedings can lead to weight loss, dehydration, hypoglycemia, and hyperbilirubinemia. **Quality and Safety: Feeding challenges place late preterm infants at risk for a prolonged hospital stay and rehospitalization** (Horgan, 2015). Lau, Bhat, Potak, and Schanler (2015) proposed a new feeding assessment tool to examine late preterm infants' oral feeding skills on their first feed to help identify infants at risk for feeding issues. It is important to evaluate feeding patterns and provide appropriate interventions as needed, which may include occupational therapy consults and lactation support (Horgan, 2015; Meier, Patel, Wright, & Engstrom, 2013).

Early and Late Neonatal Sepsis

Late preterm infants are at increased risk for infection. Late preterm deliveries can often result from preterm labor and premature rupture of membranes with the etiology of infection. These infants undergo more sepsis workups than term infants as well as more antibiotic therapy. **Quality and Safety: Providers should look at risk factors for sepsis and signs and symptoms of infection, including temperature instability, lethargy, jitteriness, irritability, hypotonia, respiratory distress, hypotension, poor perfusion, poor feedings, vomiting, diarrhea, glucose instability, rashes, and jaundice.** A CBC with differential, blood cultures, and antibiotic therapy should be implemented with signs of infection. Appropriate length of treatment of antibiotics should be determined (Ramachandrappa & Jain, 2015).

Admission to NICU and Prolonged Hospital Stay

Late preterm infants are more likely to require admission to the NICU and prolonged hospitalization compared to term infants. Admission depends on gestation age, comorbidities, and each institution's organization of care. The duration of the NICU stay is inversely proportional to gestational age. Approximately 33% of NICU admissions each year are for infants who are greater than 34 weeks' gestational age. Common reasons for infant NICU stays include RDS, poor feeding, hypoglycemia, temperature instability and hyperbilirubinemia (Horgan, 2015; Ramachandrappa & Jain, 2015).

DISCHARGE, FOLLOW-UP CARE, AND REHOSPITALIZATION OF THE LATE PRETERM INFANT

Discharge

When planning discharge transitioning to outpatient care, the process should begin on admission and requires a coordinated multidisciplinary approach. Late preterm infants should delay discharge until greater than 48 hours of age to assure infant stability. Infant stability will reflect physiologic maturity, and includes successful feeding without vomiting for at least 24 hours without excessive weight loss, normal vital signs on room air, with absence of medical illness such as no signs of infection, a risk assessment for the development of severe hyperbilirubinemia, and follow-up arranged as needed. The infant must have good temperatures in a crib and proper voiding and stooling. **Quality and Safety: A physical examination must be performed within 24 hours of discharge, with no evidence of active bleeding at the circumcision site for at least 2 hours, hepatitis B vaccine administration, metabolic screens according to state recommendations, passed car seat safety test, hearing assessment, a family environment and social risk factor assessment, and parent training.** Family teaching regarding care of the late preterm infant is essential. Pediatric follow-up 24 to 48 hours after hospital discharge is critical. Good discharge planning will allow a smooth transition for the infant from the hospital environment to home and it will also help reduce hospital readmissions (Phillips et al., 2013; Ramachandrappa & Jain, 2015).

Follow-Up Care

It is important to provide follow-up care for late preterm infants and resources for the family for healthy growth and rehospitalization prevention. Follow-up should begin in the hospital and continue once the late preterm infant is discharged (Phillips et al., 2013).

Close follow-up should be provided by the primary care provider, having a visit 24 to 48 hours after hospital discharge. The primary care provider should assess the infant's continued stability, review screening results, ensure ongoing safety, and evaluate support systems. **Quality and Safety: Late preterm infants should be followed weekly until the infant displays stability and is 40 weeks' gestation. Additional visits may be required for weight and bilirubin checks** (Phillips et al., 2013). Consultant follow-up including medical consultants, Visiting Nurses Association (VNA), and early intervention should be used as needed.

It is important for the late preterm infants' mothers to obtain breastfeeding support from the pediatric nurse practitioner and visiting nurse because often these infants are discharged early and lack sufficient time for breastfeeding support. These infants often have an immature suck and swallow pattern that can lead to poor feeding, dehydration, hyperbilirubinemia, and rehospitalization. Late preterm infants are at greater risk for breastfeeding-associated rehospitalization compared to term infants. Follow-up is critical for late preterm healthy growth and development (Ahmed, 2010; Lau et al., 2015; Radtke, 2011).

Rehospitalization

There is an increased risk for rehospitalization of late preterm infants, most often related to jaundice and feeding difficulties (Kuzniewicz, Parker, Schnake-Mahl, & Escobar, 2013; Moyer et al., 2014; Ray & Lorch, 2013). Moyer et al. (2014) found a 3.6% rehospitalization rate within the first 28 days of birth. Late preterm infants required readmission due to hyperbilirubinemia (75%), feeding difficulties (34%), hypothermia (12%), and suspected sepsis (4%). They found hyperbilirubinemia readmission occurred most often around day 4.5, feeding challenges around 10.4 days, hypothermia around 9.3 days, and suspected sepsis around 13 days.

Goyal, Zubizarreta, Small, and Lorch (2013) found a similar hospital readmission rate of 3% within 7 days of discharge. Researchers found no reduction in 7 days readmission rate associated with longer admission hospital length of stay. They suggest further research needed in this area.

Ray and Lorch (2013) studied hospital readmission of early, late preterm infants and term infants in the first year of life. Research found late preterm infants experienced an increase in prehospitalization within 14 days of discharge at 3.6%, which was similar to early preterm infants at 3.7% and term infants at 2.2%. Late preterm infants most often were readmitted for hyperbilirubinemia with bacterial and nonspecific infection as a secondary cause but far less common.

Hospital readmission rates were significantly higher for late preterm infants never admitted to the NICU. Additionally, late preterm infants who are discharged at less than 24 hours of age also had higher readmission rates (Ramachandrappa & Jain, 2015).

LONG-TERM OUTCOMES

Research has shown that late preterm infants have an increased risk of medical problems and poor health-related outcomes. They also have long-term adverse developmental outcomes including cognitive delay with poor school performance as well as social and behavioral challenges. Although the absolute risk of poor long-term outcome in the late preterm infant population is low, it is significantly higher than their term counterparts (Odibo et al., 2016; Shah, Kaciroti, Richards, Oh, & Lumeng, 2016; Vohr, 2013; Woythaler, McCormick, Mao, & Smith, 2015).

Late preterm infants in the first year of life had an increased risk for poor health-related outcomes during the birth hospitalization. Medical challenges included hyperbilirubinemia, infection, and respiratory issues including asthma. They found a statistically significant increase in healthcare utilization during the first year of life, including increased total hospital time, increased hospital and outpatient costs, as well as overall total healthcare costs (Odibo et al., 2016; Vohr, 2013).

Late preterm infants requiring NICU admission had increased need for interventional therapies: 30% required early intervention services, 28% physical therapy, 16% occupational therapy, 10% speech therapy, and 6% special education (Kalia, Visintainer, Brumberg, Pici, & Kase, 2009; Vohr, 2013). Woythaler, McCormick, and Smith (2011) found late preterm infants have a poorer developmental outcome than term infants at 24 months of age, including more mild and severe mental and psychomotor developmental delays.

Late preterm infants were found to have an increased incidence of cerebral palsy (CP), developmental delay, and mental retardation (MR). These infants were three times more likely to be diagnosed with CP than their term counterparts and at marginally higher risk for developmental delay and MR. Late preterm infants were not at increased risk for seizures, as noted in this study (Petrini et al., 2009).

Late preterm infants are at increased risk for poor school performance compared to their term counterparts (Woythaler et al., 2015). Talge et al. (2010) found late preterm infants exhibited poorer cognitive performance with IQ scores at age 6. They also found increased behavioral problems at age 6, including higher levels of internalizing and attention problems. Lipkind, Slopen, Pfieffer, and McVeigh (2012) found late preterm infants had an increased need for special education services and lower math and English scores in grade 3 when compared with term infants. Shah et al. (2016) research showed late preterm infants had poorer school performance, especially in preschool and kindergarten, with reading and math skills.

Rogers et al. (2014) found late preterm infants were at risk for altered brain development, particularly in the right temporal and parietal cortices resulting in increased rates of anxiety symptoms that persist until school age.

SUMMARY

Late preterm infant births, infants born at 34 0/7 to 36 6/7 weeks, are on the rise. Late preterm deliveries are due to spontaneous preterm labor and inductions for fetal and maternal indications. These infants are at increased risk for physiologic immaturity, as well as higher morbidity and mortality rates. They also have more medical complications, NICU admissions, and prolonged hospitalizations. It is important to understand these risks and provide closer monitoring and expert medical and nursing care, as well as stricter discharge criteria, follow-up care, and strategies to prevent rehospitalization. Late preterm infants are at increased risk for long-term sequelae. More research is needed in this population to understand how to prevent late preterm births and optimize care for successful outcomes.

CASE STUDY

■ **Identification of the Problem.** Baby boy M was born at 35 weeks' gestation and developed respiratory distress at 4 hours of life in the normal newborn nursery.

■ **Assessment: History and Physical Examination.** Baby boy M was born at 35 weeks weighing 2,090 g to a 31-year-old G1 P0 now 1, blood type A positive, antibody screen negative, rapid plasma reagin nonreactive, Rubella immune, hepatitis B surface antigen negative, HIV negative, group B streptococcus negative mother. This pregnancy was complicated by gestational diabetes, diet-controlled, and preterm labor. Maternal antibiotics were given. Labor persisted, and the infant was born by normal vaginal delivery. A nurse practitioner was at the delivery due to prematurity; the infant emerged crying and was brought to the warmer. Routine drying and stimulation was provided, and Apgars were 8 and 9. The infant transitioned nicely and was transferred to the normal nursery. At 4 hours of age, the infant was tachypneic, grunting, retracting, and flaring and requiring face mask oxygen to keep saturations above 90%. The infant was transferred to the NICU. On admission to the NICU, the baby was noted to have a hood oxygen requirement of 25%, a dextrostix of 30, and a temperature of 36°C.

■ **Physical Examination**

- GENERAL APPEARANCE: alert and active, mild distress
- HEAD: fontanelle soft and flat; no eye drainage, positive red reflex; ears normally set and rotated; nares patent; moist mucous membranes, palate intact

- SKIN: warm, well perfused, no lesions
- NECK: clavicles intact, no crepitus
- RESPIRATORY: lungs are clear to auscultation, breath sounds equal, expiratory grunting, nasal flaring, mild intercostal retractions, chest wall within normal limits, cry normal
- CARDIOVASCULAR: regular heart rate and rhythm without murmur, femoral pulses 2 plus bilaterally, well perfused, capillary refill less than 2 seconds
- ABDOMEN: soft, nontender, not distended, normal bowel sounds, no hepatosplenomegaly, three-vessel umbilical cord
- GENITOURINARY: normal male genitalia, testes descended bilaterally, anus patent
- MUSCULOSKELETAL: no sacral dimple, no hip clunk, normal upper and lower extremities
- NEUROLOGIC: alert, moving all extremities times 4, normal tone and strength, Moro complete, normal grasp and suck, no focal deficits

■ **Differential Diagnoses.** Respiratory diagnoses: respiratory distress syndrome (RDS), transient tachypnea of the newborn (TTN), pneumonia, pulmonary hypertension

- Rule out sepsis
- Hypoglycemia
- Hypothermia

■ Diagnostic Tests

- Chest radiography
- Arterial blood gas
- Blood glucose and dextrostix monitoring
- CBC with differential
- Blood culture

■ **Working Diagnosis.** Baby M had a chest x-ray with prominent perihilar interstitial markings and fluid in the minor fissure, which is most consistent with TTN. He had blood gas pH 7.40, P_{CO_2} 42, P_{O_2} 80, and a base excess of 1, which further supports the diagnosis. Baby M had a normal CBC with differential, a white blood count of 15.6, hematocrit of 17, and platelets of 211. The differential showed 46 neutrophils, 2 bands, 40 lymphocytes, 7 monocytes, and 5 eosinophils. The working diagnosis ruled out sepsis since the actual infection risk is low. The maternal group B streptococcus (GBS) status was negative, and the baby's physical examination was within normal limits except for the respiratory symptoms that point to TTN.

The dextrostix on admission to the NICU was 30. Baby M is a late preterm infant at risk for hypoglycemia due to metabolic immaturity. Additionally, baby M's mother had gestational diabetes, which puts the infant at risk for transient hypoglycemia.

Baby M had a temperature of 36°C, which is common in late preterm infants. Metabolic immaturities lead to transient hypothermia.

■ **Development of Management Plan.** The respiratory plan was to wean the oxygen as tolerated, keeping oxygen saturations greater than 90%. Baby M had an IV started due to his dextrostix of 30, given a bolus of dextrose 10 in water (2 mL/kg), and started on maintenance IV fluids (GIR 5.6 mg/kg/minute, total fluids of 80 mL/kg/day). Dextrostixs were to be performed every 1 to 3 hours until greater than 45. Baby M was placed on a warmer for his temperature of 36°C.

■ **Implementation and Evaluation of Effectiveness.** Baby M weaned to room air, and the respiratory symptoms resolved by 12 hours of life. Baby M's repeat dextrostix was 45 after the glucose bolus and IV fluids, with the resolution of the hypoglycemia. He started feeding at 24 hours of life and had difficulty with poor coordination of feeds and weight loss, which took 7 days to resolve. Baby M had difficulty maintaining his temperature and finally weaned to a crib after 4 days.

■ **Outcome.** Baby M experienced many of the typical medical complications related to late preterm infants' physiologic and metabolic immaturity, which resulted in a NICU admission and prolonged hospital stay. Baby M went home after a 7-day admission to the NICU. He will have close primary care provider follow-up to promote healthy growth and prevent rehospitalization.

EVIDENCE-BASED PRACTICE BOX

Late preterm infants are infants born between 34 0/7 and 36 6/7 weeks' gestation and are increasing in number throughout the country and around the world. These infants have higher rates of morbidity and mortality, as well as increased medical complications, NICU admissions, and prolonged hospitalization (Engle, 2011; Engle et al., 2007; Ramachandrappa & Jain, 2009). Late preterm infants require closer monitoring and specialized medical and nursing care with stricter discharge criteria and follow-up care. These infants have a higher rehospitalization rate and long-term sequelae.

It is clear that late preterm infants are different from term infants and should be monitored more closely. Late preterm infants are at increased risk for TTN, RDS, PPHN, respiratory failure, apnea, hyperbilirubinemia, hypothermia, hypoglycemia, feeding difficulties, neonatal sepsis, and NICU admission with a prolonged hospital stay as well as having mothers with increased emotional distress. These medical problems need careful assessment and treatment (Martin et al., 2011). Late preterm infants are more likely to require admission to the NICU and prolonged hospitalization compared to term infants.

When planning discharge of the late preterm infant, criteria developed for both high-risk infants and healthy term infants should be considered. Discharge for term infants after a vaginal delivery is typically less than 48 hours. In 1995 with a revision in 2004, the AAP recommended a minimum eligibility of 38 to 42 weeks' gestation as discharge criteria for early discharge, less than 48 hours (AAP, Committee on Fetus and Newborn, 1995, 2004). Goyal et al. (2011) found 40% of late preterm infants were discharged early, prior to 48 hours. The AAP continues to recommend discharge after 48 hours.

(*continued*)

EVIDENCE-BASED PRACTICE BOX (*continued*)

Engle et al. (2007) have recommended discharge criteria that reflect evidence of physiologic maturity, feeding competences, thermoregulation, maternal education, assessment, and planned intervention for medical, family, environmental, and social risk factors, and follow-up arrangements. Important minimal discharge criteria should include the following: accurate gestational age determination, meeting of feeding-based competencies, thermoregulation and absence of medical illness, and social risk factors (usually after 48 hours); pediatric follow-up 24 to 48 hours after hospital discharge; vital signs within the normal range for 12 hours preceding discharge; passage of at least one stool spontaneously; 24 hours of successful feeding; a risk assessment for the development of severe hyperbilirubinemia and follow-up arranged as needed; physical examination with no abnormalities requiring hospitalization; no evidence of active bleeding at circumcision site for at least 2 hours, hepatitis B vaccine administration or an appointment for administration; metabolic screens according to state recommendations, passed car seat safety test; hearing assessment; family environment and social risk factor assessment, and parent training (AAP Committee on Fetus and Newborn, 2008; Engle, 2011; Martin et al., 2011).

Good discharge planning will allow a smooth transition for the infant from the hospital environment to home. It will also help reduce hospital readmissions.

Reference

American Academy of Pediatrics Committee on Fetus and Newborn. (1995). Hospital stay for healthy term newborns. *Pediatrics, 96*(4 pt 1), 788–790.

American Academy of Pediatrics Committee on Fetus and Newborn. (2004). Hospital stay for healthy term newborns. *Pediatrics, 113*(5), 1434–1436.

Engle, W. A., Tomashek, K. M., Wallman, C., & The Committee on Fetus and Newborn. (2007). "Late-preterm" infants: A population at risk. *Pediatrics, 120*(6), 1390–1401.

Goyal, N. K., Fager, C., & Lorch, S. A. (2011). Adherence to discharge guidelines for late-preterm newborns. *Pediatrics, 128*(1), 62–71.

Martin, J. A. (2011). Preterm births-United States, 2007. *Morbidity & Mortality Weekly Report, 60*, 78–79.

Ramachandrappa, A., & Jain, L. (2009). Health issues of the late preterm infant. *Pediatric Clinics of North America, 56*(3), 565–567. doi:10.1016/j.pcl.2009.03.009

PARENT VOICES

Crystal Duffy

To be a parent of a late preterm infant in the NICU is like being pushed aside, left on your own, and disregarded because your baby is doing "great." We must not forget that every patient no matter if they spend 4 hours in the NICU or 18 months, should receive the same compassion and quality of care.

ONLINE RESOURCES

Association of Women's Health, Obstetric and Neonatal Nurses. (n.d.). *AWHONN Late Preterm Infant Initiative®*. Retrieved from https://www.awhonn.org/page/AWHONNLateInfant/AWHONN-Late-Preterm-Infant-Initiative.htm

Barfield, W. D., & Lee, K. G. (2019). Late preterm infants. In M. S. Kim (Ed.), *UpToDate*. Retrieved from https://www.uptodate.com/contents/late-preterm-infants

Bird, C. (2018, July 9). Overview of late preterm infant health. *Very Well Family*. Retrieved from https://www.verywellfamily.com/health-concerns-of-the-late-preterm-infant-2748610

Council of International Neonatal Nurses. (2010). *Position statement on care of the late preterm infant*. Retrieved from https://coinnurses.org/wp-content/uploads/2013/06/Position_Stat_Late_Preterm.pdf

REFERENCES

Ahmed, A. H. (2010). Role of the pediatric nurse practitioner in promoting breastfeeding for late preterm infants in primary care settings. *Journal of Pediatric Health Care, 24*(2), 116–122. doi:10.1016/j.pedhc.2009.03.005

Cheng, Y. W., Kaimal, A. J., Bruckner, T. A., Halloran, D. R., & Caughey, A. B. (2011). Perinatal morbidity associated with late preterm deliveries compared with deliveries between 37 and 40 weeks of gestation. *BJOG: An International Journal of Obstetrics and Gynecology, 118*(12), 1446–1454. doi:10.1111/j.1471-0528.2011.03045.x

Crump, C., Sundquist, K., Sundquist, J., & Winkleby, M. A. (2011). Gestational age at birth and mortality in young adulthood. *Journal of American Medical Association, 306*(11), 1233–1240. doi:10.1001/jama.2011.1331

Goyal, N., Zubizarreta, J. R., Small, D. S., & Lorch, S. H. (2013). Length of stay and readmission among late preterm infants: An instrument variable approach. *Hospital Pediatrics, 3*(1) 7–15. doi:10.1542/hpeds.2012-0027

Gyamfi-Bannerman, C. (2012). Late preterm birth: Management dilemmas. *Obstetric and Gynecology Clinics, 39*(2), 35–45. doi:10.1016/j.ogc.2011.12.005

Horgan, M. J. (2015). Management of the late preterm infant: Not quite ready for prime time. *Pediatric Clinics of North America, 62*(2), 439–451. doi:10.1016/j.pcl.2014.11.007

Kalia, J. L., Visintainer, P., Brumberg, H. L., Pici, M., & Kase, J. (2009). Comparison of enrollment in interventional therapies between late-preterm and very preterm infants at 12 months' corrected age. *Pediatrics, 123*(3), 804–809. doi:10.1542/peds.2008-0928

King, J. P., Gazmarian J. A., & Shapiro-Mendoza, C. K. (2014). Disparities in mortality rates among US infants born late preterm or early term, 2003-2005. *Maternal Child Health Journal, 18*(1), 233–241. doi:10.1007/s10995-013-1259-0

Kuzniewicz, M. W., Parker, S., Schnake-Mahl, A., & Escobar, G. J. (2013). Hospital readmissions and emergency department visits in moderate preterm, late preterm, and early term infants. *Clinics of Perinatology, 40*(4) 753–775. doi:10.1016/j.clp.2013.07.008

Lau, C., Bhat, K., Potak, D., & Schanler R. J. (2015). Oral feeding assessment predicts length of hospital stay in late preterm infants. *Journal of Pediatric Mother Care, 1*(1), 102. doi:10.19104/japm.2016.102

Lipkind, H. S., Slopen, M. E., Pfeiffer, M. E., & McVeigh, K. H. (2012). School-age outcomes of late preterm infants in New York City. *American Journal of Obstetrics and Gynecology, 206*(3), e1–e6. doi:10.1016/j.ajog.2012.01.007

Mally, P. V., Hendricks-Munos, K. D., & Baily, S. (2013). Incidence and etiology of late preterm admissions to the neonatal intensive care unit and its associated respiratory morbidities when compared to term infants. *American Journal of Perinatology, 30*(5), 425–431. doi:10.1055/s-0032-1326989

March of Dimes. (2017). *U.S. preterm birth rate on the rise for second year in a row: 2017 March of Dimes premature birth report card*. Retrieved from https://www.marchofdimes.org/news/u-s-preterm-birth-rate-on-the-rise-for-second-year-in-a-row.aspx

Meier, P., Patel, A. L., Wright, K., & Engstrom, J. L. (2013). Management of breastfeeding during and after the maternity hospitalization for late preterm infants. *Clinic of Perinatology, 40*(4), 689–705. doi:10.1016/j.clp.2013.07.014

Mohan, S. S., & Jain, L. (2011). Late preterm birth: Preventable prematurity? *Clinics in Perinatology, 38*(3), 547–555. doi:10.1016/j.clp.2011.06.005

Montenegro, B. L., Amberson, M., Veit L., Freiberger, C., Dukhovny D., & Rhein, L. M. (2017). Economics of home monitoring for apnea in late preterm infants. *Respiratory Care, 62*(1), 42–48. doi:10.4187/respcare.04954

Moyer, L. B., Goyal, N. K., Meinzen-Derr, J., Ward, L. P., Rust, C. L., Wexelblatt, S. L., & Greenberg, J. M. (2014). Factors associated with readmission in late-preterm infants: A matched case-control study. *Hospital Pediatrics, 4*(5), 298–304. doi:10.1542/hpeds.2013-0120

Murphy, S. L., Mathews, T. J., Martin, J. A., Minkovitz, C. S., & Strobino, D. M. (2017). Annual summary of vital statistics: 2013–2014. *Pediatrics, 139*(6), e20163239. doi:10.1542/peds.2016-3239

Odibo, I. N., Bird, T. M., McKelvey, S., Sandlin, A., Lowery, C., & Magann, E. F. (2016). Childhood respiratory morbidity after late preterm and early term delivery: A study of Medicaid patients in South Carolina. *Pediatric and Perinatal Epidemiology, 30*(1), 67–75. doi:10.1111/ppe.12250

Petrini, J. R., Dias, T., McCormick, M. C., Massolo, M. L., Green, N. S., & Escobar, G. J. (2009). Increased risk of adverse neurological development for late preterm infants. *Journal of Pediatrics, 154*(2), 169–176.e3. doi:10.1016/j.jpeds.2008.08.020

Phillips, R. M., Goldstein, M., Hougland, K., Nandyal, R., Pizzica, A., Santa-Dlonato, A., … Yost, E. (2013). Multidisciplinary guidelines for the care of late preterm infants. *Journal of Perinatology, 33*(Suppl. 2), S3–S4. doi:10.1038/jp.2013.52

Radtke, J. V. (2011). The paradox of breastfeeding-associated morbidity among late preterm infants. *Journal of Obstetric, Gynecologic, & Neonatal Nursing, 40*(1), 9–24. doi:10.1111/j.1552-6909.2010.01211.x

Raju, T. N. (2017). The "Late Preterm" birth—Ten years later. *Pediatrics, 139*(3), e20163331. doi:10.1542/peds.2016-3331

Raju, T. N., Higgins, R. D., Stark, A. R., & Leveno, K. J. (2006). Optimizing care and outcome for late-preterm (near-term) infants: A summary of the workshop sponsored by the National Institute of Child Health and Human Development. *Pediatrics, 118*(3), 1207–1214. doi:10.1542/peds.2006-0018

Ramachandrappa, A., & Jain, L. (2009). Health issues of the late preterm infant. *Pediatric Clinics of North America, 56*(3), 565–567. doi:10.1016/j.pcl.2009.03.009

Ramachandrappa, A., & Jain, L. (2015). The late preterm infant. In R. J. Martin, A. A. Fanaroff, & M. Walsh (Eds.), *Fanaroff and Martin's neonatal-perinatal medicine: Diseases of the fetus and infant* (10th ed., pp. 577–591). Philadelphia, PA: Elsevier Mosby.

Ray, K. N., & Lorch, S. A. (2013). Hospitalization of early preterm late preterm and term infants during the first year of life by gestational age. *Hospital Pediatrics, 3*(3), 194–203. doi:10.1542/hpeds.2012-0063

Rogers, C. E., Barch, D. M., Sylvester, C. M., Pagliaccio, D., Harms, M. P., Botteron, K. N., & Luby, J. L. (2014, August 6) Altered grey matter volume and school age anxiety in childrenborn late preterm. *Journal of Pediatrics, 165*(5), 928-935 doi:10.1016/j.jpeds.2014.06/063

Shah, P., Kaciroti, N., Richards, B., Oh, W., & Lumeng, J. C. (2016). Developmental outcomes of late preterm infants from infancy to kindergarten. *Pediatrics, 138*(2), e20153496. doi:10.1542/peds.2015-3496

Shapiro-Mendoza, C. K., & Lackritz, E. M. (2012). Epidemiology of late and moderate preterm birth. *Seminars in Fetal and Neonatal Medicine, 17*(3), 120–125. doi:10.1016/j.siny.2012.01.007

Talge, N. M., Holzman, C., Wang, J., Lucia, V., Gardiner, J., & Brreslau, N. (2010). Later-preterm birth and its association with cognitive and socioemotional outcomes at 6 years of age. *Pediatrics, 126*(6), 124–132. doi:10.1542/peds.2010-1536

Vink, J., & Gyamfi-Bannerman, C. (2017). Current preterm birth prevention strategies. *Seminars in Perinatology, 41*(7), 385–386. doi:10.1053/j.semperi.2017.07.016

Vohr, B. (2013). Long-term outcomes of moderately preterm, late preterm and early term infants. *Clinics in Perinatology, 40*(4), 739–751. doi:10.1016/j.clp.2013.07.006

Woythaler, M., McCormick, M. C., Mao, W., & Smith, V. C. (2015). Late preterm infants and neurodevelopmental outcomes at kindergarten. *Pediatrics, 136*(3), 424–431. doi:10.1542/peds.2014-4043

Woythaler, M. A., McCormick, M. C., & Smith, V. C. (2011). Late preterm infants have worse 24 month neurodevelopmental outcomes than term infants. *Pediatrics, 127*(3), e622–e629. doi:10.1542/peds.2009-3598

CHAPTER 30

Neonatal Abstinence Syndrome

Gail A. Bagwell

INTRODUCTION

Opiate addiction and neonatal abstinence syndrome (NAS) have become major health problems for pregnant women and neonates in the United States. NICU and special care units (SCN) have been inundated with babies that are withdrawing not only from opiates but from other licit and illicit substances that they were exposed to in-utero. This chapter discusses the history, incidence, and diagnosis of NAS, the screening tools, and nonpharmacological and pharmacological management involved, the importance of nonjudgmental care of the mother–infant dyad, and the long-term outcomes of the NAS neonate.

HISTORY OF OPIATE ADDICTION

Opioid use during pregnancy is not a new phenomenon in the United States. Opioid addiction in the United States is as old as our country is, as it dates back to the American Revolution where both American and British soldiers were given opium for illness and injuries (Courtwright, 2001). With the discovery of morphine in 1803 and then the invention of the hypodermic syringe and needle in 1856, many feel that the first true opiate addiction occurred with the Civil War in the United States. Morphine was used like opium was in the American Revolution, for the sick and injured soldiers, but was also used to treat diseases of the uterus, ovaries, and nervous conditions of women. Morphine during this time did not require a prescription, so it was readily used. By 1895, one in 200 Americans had an opiate addiction problem, with 60% of them being upper-class or middle-class white women (Courtwright, 2001). The use of morphine for women was largely due to a lack of understanding and training by physicians at the time; as medical education became more rigorous and knowledge of problems increased, and with the release of a new analgesic called aspirin in 1897, the use of morphine decreased. While the opiate addiction problem didn't go away, the addict profile changed from war veterans and upper-class or middle-class white women to lower-class males and new immigrants, with the opening of opium dens in America in the early 1900s. With the changing profile of the addict, legal ramifications began to take hold in the United States making possession of opium and heroin illegal, but these did not deter use.

In the 20th century, the heroin epidemic in the 1950s and 1960s brought attention to drug use by pregnant women and concern about the effects of drugs on the developing fetus. In the late 1970s and the 1980s, heroin fell out of favor and cocaine became an issue, but by the 2000s heroin started to gain popularity again.

The resurgence of heroin is attributed in large part to the prescription drug abuse that began in the 1990s. Simultaneously several events occurred that led to prescription drug abuse: The Joint Commission instituted the mandatory assessment of pain as the fifth vital sign; a new opiate medication, oxycodone, was promoted to practitioners as a nonaddictive opiate analgesic; insurance companies tightened their belts on what nonpharmacological treatments that they would pay for, limiting what a practitioner could do for patients in acute pain; and healthcare practitioners and healthcare facilities began patient satisfaction surveys. These events resulted in practitioners overprescribing oxycodone and other narcotics to patients, which led many to addiction, as we now know that oxycodone is as powerful as or more powerful than heroin (Quinones, 2015).

The Center for Behavioral Health Statistics and Quality (CBHSQ) estimated that in 2015, 27 million people were abusing illicit or prescription drugs. As in previous opiate epidemics, women of childbearing age were not immune to the problem. For women of childbearing age (ages 15–44), the CBHSQ (2016) reported that heroin use increased by 31% from 2011–2012 to 2013–2014 and that there was a 5.3% increase in the number of women who reported OxyContin misuse during the same time periods.

HISTORY AND EPIDEMIOLOGY OF NEONATAL ABSTINENCE SYNDROME

A consequence of the opiate epidemic is the exposure of the fetus in-utero to opiates, which results in neonates withdrawing from the substance after birth. This is referred to as neonatal abstinence syndrome or NAS, which is not a new phenomenon. The term NAS was first coined by Dr. Loretta Finnegan and her colleagues in the early 1970s to describe neonates they were caring for who were withdrawing from heroin and other opiates, but the term now includes neonates withdrawing from other substances as well. However, this was not the first description in medical literature of neonates withdrawing from substances.

The first descriptions of this phenomenon appeared in medical publications as early as 1875 under the term *congenital morphinism* (Perlstein, 1947). With the morphine epidemic described earlier, there were documented cases of neonates dying several days after birth, even though they appeared normal at birth. The case reports described neonates displaying the signs of what we today call NAS.

As the opioid epidemic increased in the early 2000s, NICUs and special care units (SCNs) began to see an explosion of neonates being admitted for NAS. In a first-of-its-kind article on the epidemic of NAS, Patrick et al. (2012) did a retrospective, cross-sectional analysis of data from the Centers for Medicare and Medicaid (CMS) of neonates diagnosed with NAS from 2000 to 2009 in the United States, to determine the prevalence of NAS. The investigators found that the number of neonates experiencing NAS increased from approximately 1.3 per 1,000 births in 2000 to approximately 3.4 per 1,000 births in 2009. The number of neonates tripled in 9 years from approximately 4,000 to approximately 13,539 neonates or approximately one neonate being born every hour with NAS (Patrick et al., 2012).

A follow-up study by Patrick, Davis, Lehmann, and Cooper (2015) revealed that the numbers of babies being diagnosed with NAS continued to increase from 2009 to 2012. In the 2015 study, the investigators also looked at the regional prevalence of NAS and found that it varied from 2.6 per 1,000 births to 16.2 per 1,000 births based on geographical location. The overall incidence of NAS in 2012 was 5.8 per 1,000 births, equivalent to 21,732 births or one baby born every 25 minutes. Most recently, Winkelman, Villapiano, Kozhimannil, Davis, and Patrick (2018) reported that in 2014 the overall incidence of NAS in the United States was 14.4 per 1,000 births or one baby being born every 15 minutes.

As the number of babies being diagnosed with NAS increased, mother/baby units were not equipped to care for the withdrawing infant, so the majority of the neonates affected were transferred to NICUs and SCNs to be observed and treated. Tolia et al. (2015) reported that the number of NICU admissions increased from seven per 1,000 admissions in 2004 to 27 per 1,000 admissions in 2013, putting a strain on NICUs and SCNs around the country by taking up valuable bed space and utilizing resources designed for ill neonates, neonates with congenital defects, and premature infants.

The increasing numbers of neonates with NAS that are being born in the United States has put a strain not only on hospitals, but also on the healthcare system. In 2014, approximately 82% of all neonates with NAS were covered by Medicaid, up from 73.7% a decade earlier in 2004. Neonates with an NAS diagnosis that were Medicaid recipients had longer hospital stays than neonates with NAS that were covered by private insurance and neonates covered by Medicaid who did not have NAS. As a result of the increasing number of Medicaid-covered neonates, hospital costs increased from $65.4 million to $462 million during the 10-year period from 2004 to 2014, putting a strain on many systems (Winkelman et al., 2018).

DIAGNOSIS

Diagnosis of NAS begins with a thorough checking of maternal history of any substance usage during the pregnancy. A policy of universal screening for all pregnant women should be in place in physician offices, hospitals, and birthing centers, as substance abuse occurs across all socio-economic classes. Many confuse screening with testing pregnant women for a substance abuse problem and believe the terms are interchangeable, which they are not. Screening is different from testing, as it consists of interviewing pregnant women for use of both legal and illicit substances, while testing involves checking for presence or absence of substances in biological fluids.

Maternal Screening

When screening the pregnant woman, the interview should be done in a nonjudgmental manner and in a private setting, away from family members and friends. This is done as many family members and friends may be unaware of a woman's substance usage or may not want the woman to divulge this information for fear of consequences. The interview questions should include the use of five types of substances: (1) prescription drugs; (2) over-the-counter drugs; (3) nutritional supplements, including herbal medications; (4) legal substances, such as alcohol, nicotine, and caffeine; and (5) illicit/illegal drugs. In addition to the type of substance/drug used, the length of use, the amount used, the method of use, the context of use, and any history of drug treatment is essential. For women who do not admit to drug use, a history of drug habits of family members and friends should be obtained, as often a woman may admit to a family member's use/abuse, but not to her own abuse.

There are many tools available to assist with screening patients with substance use disorders such as the Alcohol Use Disorders Intervention Test-C, (AUDIT-C), National Institute on Drug Abuse (NIDA) Drug Use Screening Tool and Quick Screen, Opioid Risk Tool, Screening to Brief Intervention (S2BI), Brief Screener for Alcohol, Tobacco, and other Drugs (BSTAD), CAGE, and the Car, Relax, Forget, Friends, Trouble (CRAFFT). The BSTAD, CRAFFT, and S2BI are designed specifically for adolescents and the remaining tools are designed for adults, though the NIDA test does have an adaptation for adolescents (NIDA, 2018). The choice of the correct tool is based on the age of the clientele and what the clinician needs to assess. Regardless of the tool chosen, it is important to use an evidence-based and validated tool, which all of the previously noted items are, and to ask the questions in a nonjudgmental manner and environment.

One method to assist with obtaining information from a client is motivational interviewing (MI). MI was developed in the 1980s by Miller and Rollnick based on the work by Carl Rogers as a way to elicit information from a client and to begin the change process (Substance Abuse and Mental Health Services Administration-Health Resources and Services Administration [SAMHSA-HRSA] Center for Integrated Health Solutions, n.d.). MI utilizes the four principles of expressing empathy and avoiding arguing, developing discrepancy, rolling with resistance, and supporting self-efficacy. For the interviewer to be successful in using the MI technique he or she must listen more than talk, be sensitive and open to the person's issue, invite the person to be open and to discuss and explore ideas of change, encourage the person to discuss reasons not to change, ask for permission to give his or her feedback, reassure the mother that ambivalence to change is normal, help the mother identify successes and challenges, seek to understand the person, summarize what he or she is hearing, value the person's opinion, and remind oneself that the person is capable of making her own choices (SAMHSA-HRSA Center for Integrated Health Solutions, n.d.).

Maternal Testing

Urine drug testing can be ordered to help with the detection of a substance abuse disorder. Maternal urine toxicology is easy to obtain, but is not always accurate. Women with substance use disorder have a fear of losing their babies and will go to great lengths to hide their substance use. The half-life of substances of abuse varies, so depending on the timing of the urine drug test, the urine may or may not be positive. Women with substance abuse disorder also know methods to ensure that the urine drug test has a false negative. A quick search online will show novel ways to pass a urine drug test, ranging from devices that could be used,

information on how long substances are detectable, and how to clear the urine of substances. For these reasons, the maternal urine drug test could be negative, even though there is a substance abuse disorder. In addition, it is important to remember that maternal drug testing has legal implications if not all pregnant women admitted to a hospital or in a medical practice are tested, as it could be considered profiling. Because of the legal issues to testing only certain individuals, many medical practices and hospitals are adopting universal drug testing protocols for all pregnant women.

Neonatal Testing

When a baby is symptomatic of NAS or there are indicators that the mother is abusing substances, laboratory tests can be ordered to help with diagnosis of NAS. Toxicology tests can be performed on neonatal urine, hair, meconium, or the umbilical cord. Each of these tests has their pros and cons related to their use, as well as legal implications. Neonatal urine toxicology is the easiest to obtain, but is not always accurate. Neonatal urine has several limitations, some of which are: (1) only recent drug use can be detected, so if the first urine is not caught, the test may be negative, (2) if the mother is an infrequent user, the drug test may be negative, or (3) if the mother has not used in the week prior to delivery of the infant, the test may be negative depending on the drug abused and its half-life (Hudak & Tan, 2012; Kocherlakota, 2014; Kwong & Ryan, 1997; Ostrea, Chavez, & Strauss, 1976; Sutter, Leeman, & Hsi, 2014). If the urine drug test is positive, it is important to review the mother's medication record during delivery, as narcotics given to the mother during labor will show up in the neonate's urine.

Hair testing for drug use is more accurate than urine drug testing as it can detect in-utero drug usage for the last 3 to 4 months of pregnancy (Kwong & Ryan, 1997; Ostrea et al., 1976; Vinner et al., 2003). Hair testing is rarely used in the neonatal population as most newborns do not have the quantity of hair needed to perform the test and for those who do, the mothers object to their newborns' hair being shaved (Kwong & Ryan, 1997).

Meconium analysis is the most common form of drug testing in the neonate and is considered the gold standard. Meconium analysis detects in-utero drug usage for the last two trimesters of pregnancy (Kocherlakota, 2014; Ostrea et al., 1976). Unfortunately meconium is not always properly collected and stored in many units, leading to false negative results. For meconium to be accurate, the entire column of meconium must be collected and stored in a specimen cup. Substance metabolites in meconium are stable for 2 weeks at room temperature but storing it in a refrigerator is preferable. When adding meconium to the specimen cup, the new meconium sample needs to be mixed with the existing sample to ensure that the metabolites are well distributed when the lab takes only one small sample for testing. **Quality and Safety: When the entire column of meconium has been passed and collected, the specimen is sent to the lab to be tested. The lab will only take a small sample (2–5 g) to be tested, which is why it is important to mix all the meconium as it is added to the specimen cup.** While meconium is more accurate, it has its limitations. As stated before, if it is not collected correctly, false negatives will occur. Second, if the baby is not suspected of being exposed in-utero, not all of the meconium will be able to be collected. Thirdly, a specimen can be negative even if the mother abused drugs during pregnancy, depending on when and how often the mother abused drugs (Kocherlakota, 2014). Finally, in the case of babies that room-in with their mothers, meconium samples can be missed as the parents will throw the diapers away.

Umbilical cord testing for drug exposure in-utero is a newer method of testing for maternal drug usage. Like hair and meconium, the umbilical cord test is highly reliable and can detect the last 4 to 5 months of maternal drug usage (United States Drug Testing Laboratories [USDTL], n.d.). The advantage of the use of the umbilical cord is the initial availability and ease of collection. A 6-inch segment of cord is obtained at birth, drained of blood, cleansed per company protocol, labeled, sealed, and stored. The cord can be stored for a week at room temperature, refrigerated for up to 3 months, or frozen for up to 1 year (USDTL, n.d.), so if a baby starts to show signs of withdrawal, the cord can be sent at that time. The disadvantage is that if the cord is not obtained at the time of birth, then it cannot be used.

Quality and Safety: It is important to remember that no matter what type of specimen testing is done on a neonate, the appropriate chain of custody is maintained during the collection, labeling, and transport of the specimen from the unit to the laboratory. This is important for legal purposes.

Signs of NAS

Of neonates exposed to substances in-utero, approximately 55% to 96% will display signs of withdrawal (Hudak & Tan, 2012). For the majority of neonates, the onset of the acute signs of NAS can range from 12 to 96 hours after birth, though there are some cases reported of neonates beginning withdrawal only 7 days after birth. The wide range of time for withdrawal is related to the substance used, the timing of the last dose, maternal metabolism, the placental transport of the medication, as well as the neonatal gestation, metabolism, and excretion. The central and autonomic nervous systems, the gastrointestinal system, and/or the respiratory system can be involved in the withdrawal process (Finnegan & MacNew, 1974; Hudak & Tan, 2012). Table 30.1 outlines the most commonly seen signs of withdrawal in the neonate.

Not every neonate exposed to substances in-utero will show signs of withdrawal. It has been well established that term neonates experience more significant withdrawal than preterm neonates, likely due to less exposure and a more immature nervous system (Hudak & Tan, 2012; Liu, Jones, Murray, Cook, & Nanan, 2010). But other differences in withdrawal have been noted between males and females, between the type of substance exposure in-utero, and more recently the finding of genetic polymorphisms. Studies are just beginning to be published on these differences. In a recent retrospective cohort study published in 2017, Charles et al. demonstrated that male neonates were more likely than female

TABLE 30.1

WITHDRAWAL SIGNS OF NEONATAL ABSTINENCE SYNDROME

Central nervous system	High-pitched continuous crying, irritability, tremors, hyperactive Moro reflex, sleep disturbances, increased muscle tone, skin excoriation, myoclonic jerking, and seizures
Autonomic nervous system	Fever, diaphoresis, mottling, sweating, and yawning
Gastrointestinal system	Excessive sucking, poor feeding, regurgitation, vomiting, and loose or watery stools
Respiratory system	Tachypnea with or without retractions, sneezing, nasal flaring, nasal stuffiness

neonates to be diagnosed with NAS and require treatment, though the severity of NAS was not affected by gender. Huybrechts et al. (2017) found in an observational cohort study that neonates exposed to antidepressants, benzodiazepines, and gabapentin had a 30% to 60% increase of NAS when compared to those infants that were not exposed.

A newer area of study in both addiction medicine and the study of NAS is the role of genetics. In adults, single nucleotide polymorphism (SNP) in the mu-opioid receptor (*OPRM1*), catechol-*o*-methyltransferase (*COMT*), and multidrug resistance (*ABCB1*) genes are associated with the risk of addiction (Wachman, Hayes, & Brown, 2013). The authors did a multicenter prospective cohort study looking at DNA samples for variants in the SNPs of the *OPRM1*, *COMT*, and *ABCB1* genes of babies diagnosed with NAS. The results were that neonates with variants in the SNP of the *OPRM1* and *COMT* genes had significantly shorter lengths of hospital stay and a decreased need for medication therapy than those infants without. The *ABCB1* SNP did not make a difference in the length of stay or medication therapy (Wachman et al., 2013). In another study, Mactier, McLaughlin, Gillis, and Osseton (2017) looked for variations in neonate genotype of the *OPRM1*, *ABCB1*, *COMT*, *CYP2B6*, and *CYP2D6* genes as an explanation for the variation in the presentation of neonates whose mothers were maintained on methadone during pregnancy. The authors demonstrated that neonates treated for NAS were more likely to carry the homozygous allele of the *CYP2B6* gene. This new information on how genes can influence NAS could lead to more tailored approaches in caring for the NAS neonate in the near future.

With the increasing incidences of NAS, it is easy to forget that the signs of NAS are somewhat generalized and that other disease processes have similar signs. **Emergency Alert: Sepsis, hypoglycemia, and hypocalcemia have similar signs in newborns, so it is of utmost importance to rule these out before assuming that a neonate has NAS.**

Tools for Assessing Signs of NAS

Several tools have been designed over the years to help quantify the onset and progression of signs of NAS, as well as to judge the effectiveness of both nonpharmacological and pharmacological treatment. The most commonly used tool is the Finnegan Neonatal Abstinence Scoring System (FNASS), more commonly referred to as the Finnegan (Bagley, Wachman, Holland, & Brogly, 2014; Gomez-Pomar & Finnegan, 2018). The development of multiple tools over the years demonstrates the lack of agreement on how to best assess NAS. The majority of tools have been validated for interrater reliability and sensitivity to diagnosing NAS. Due to the subjective nature of the tools, especially the FNASS, it is essential for nurses to be trained on how to properly use a tool. One method for maintaining reliability in a nurse's assessment is to have nurses do dual scoring of an infant at least two times per day, which helps to maintain interrater reliability.

The tools range from the FNASS, which assesses for 21 different neurological, autonomic, gastrointestinal, respiratory, and other signs to determine if a neonate is withdrawing, to a relatively simple newer tool called ESC that looks at three items to determine treatment for withdrawal—Is the baby eating at least 1 oz or breastfeeding well? Is the baby sleeping greater than or equal to 1 hour and can the baby be consoled within 10 minutes? (Finnegan, Cron, Connaughton, & Emich, 1975; Grossman, Lipshaw, Osborn, & Berkwitt, 2018). Table 30.2 compares the published tools for assessing NAS. Studies looking at novel ways such as maternal vagal tone, fetal heart rate, skin conductance of the neonate, and brain-derived neurotropic factor levels within 48 hours of NICU admission have been done to assess and diagnose NAS, but at this point these are not widely used (Wachman, Schiff, & Silverstein, 2018).

MANAGEMENT

Once the infant is diagnosed with NAS, management focuses on the prevention or worsening of withdrawal signs and the provision of comfort for the neonate. Both nonpharmacological and pharmacological treatment options are available to manage the neonate with NAS. As more research becomes available on the detrimental effects of opioids and other medications on the developing newborn brain, the trend for treatment of babies with NAS is to do as much nonpharmacological treatment as possible before beginning pharmacological treatment.

Nonpharmacological

Initially nonpharmacological interventions such as low lighting and noise levels, skin-to-skin care by the mother, as well as swaddling and holding the baby are utilized to help control the symptoms and provide comfort to the infant experiencing NAS. Studies on nonpharmacological interventions have been done, and many of the interventions such as breastfeeding and rooming-in demonstrate a decreased length of hospital stay and symptoms of NAS, but it is important to remember that the studies are usually small with low-quality evidence (Wachman et al., 2018). Box 30.1 has a list of nonpharmacological interventions that have been published that are currently being used to help the NAS neonate.

The method of feeding and type of feeding that the neonate receives has been shown to help alleviate the symptoms of NAS and is considered a nonpharmacological intervention. Research has demonstrated that breastfeeding can decrease the severity of symptoms of NAS and shorten the length of pharmacological treatment and hospital stay. Breastfeeding, which is the optimal source of nutrition for all newborns, is recommended by the American Academy of Pediatrics (AAP) for newborns of mothers in methadone or buprenorphine treatment programs (Hudak & Tan, 2012). Studies have shown that breastfeeding increases maternal attachment and compliance in drug treatment programs, while it decreases the symptoms of NAS and the length of hospital stay for infants with NAS (McQueen, Murphy-Oikonen, Gerlach, & Montelpare, 2011; Pritham, Paul, & Hayes, 2012; Short, Gannon, & Abatemarco, 2016). However, breastfeeding rates among this group of women are low. Wachman, Byun, and Philipp (2010) found that of the 68% of women in a methadone treatment program who qualified for breastfeeding, only 24% breastfed their infants to some extent during hospitalization and 60% discontinued in an average of 5.88 days. Reasons given for less breastfeeding among women in methadone treatment programs include: (1) the lack of clear, consistent guidelines for breastfeeding mothers, (2) inconsistent advice from healthcare providers, (3) infant feeding problems due to drug withdrawal, (4) separation of the mother–infant dyad because of hospitalization, (5) mother's low self-esteem, lack of knowledge, feelings of guilt, and (6) inadequate support from healthcare providers (Jansson, Choo, Velez, Lowe, & Huestis, 2008; McQueen et al., 2011). Another factor that can affect a woman with a substance abuse disorder and her ability to breastfeed is her past history with sexual abuse. While breastfeeding is often perceived as a pleasurable experience for women, for those with a history of sexual abuse as a child, an adult, or during the pregnancy, negative feelings and reflections of the past abuse can arise and deter breastfeeding (Jansson, Velez, & Butz, 2017).

The advantages of breastfeeding (i.e., better mother–infant bonding, fewer withdrawal symptoms, and a shorter length of

TABLE 30.2

COMPARISON OF NEONATAL ABSTINENCE SCORING TOOLS

Name of Tool	Author	Year Published	Items Scored	Range of Scores	Treatment Score
FNASS	Finnegan et al.	1975	21	Severity ranges from 0 to 5	Three continuous scores ≥8 or two continuous scores ≥12
Narcotic Withdrawal Score	Lipsitz	1975	11	0–3	≥4
Neonatal Narcotic Withdrawal Index	Green & Suffett	1981	7, with seventh item being "other," which consists of 12 items	0–2	5 or greater
Ostrea	Ostrea	1976	6	Ranking of symptoms	
Neonatal Withdraw Inventory	Zahorodny et al.	1998	8	0–4	Three continuous scores ≥8 or two continuous scores ≥12
MOTHER NAS Scale	Jones et al.	2010	19	0–8	Two continuous scores ≥9 or one score ≥13
FNASS—Short Form	Maguire, Cline, Parnell, & Tai	2013	7	0–5	Three continuous scores ≥8 or two continuous scores ≥12
sFNASS	Gomez-Pomar et al.	2017	10	0–5	Three continuous scores ≥6 or two continuous scores ≥10
ESC	Grossman et al.	2018	3	Yes or no to questions	Algorithm to determine treatment based on answers

hospital stay) fuel the recommendation of the AAP, the Academy of Breastfeeding Medicine (ABM), and the American College of Obstetricians and Gynecologists (ACOG) to encourage breastfeeding among mothers who are free of other drugs in methadone and buprenorphine treatment programs and are HIV negative (ACOG, 2017; Chantry, Eglash, & Labbok, 2015; Hudak & Tan, 2012).

For those who are unable to breastfeed or choose not to breastfeed their babies, the choice of the formula that is offered to the infant, in terms of its calorie and lactose content, has generated some discussion among those treating such infants. While no randomized controlled trial studies have been done on this topic, observational studies, expert opinion, and quality improvement projects have been published. The Ohio Children's Hospital Consortium noted through observation that babies who were fed 22 calorie, low-lactose formula did better than those babies who were fed regular-lactose, 19 calorie formula (Hall et al., 2014, 2015).

In an orchestrated testing quality improvement project done by the Ohio Perinatal Quality Collaborative (OPQC), a 22 calorie/oz formula has been found to help with the alleviation of NAS symptoms, regardless of lactose content. The orchestrated testing comprised of putting the 54 hospitals participating in the quality improvement project into four types of feeding groups. The groups were low lactose 19 calorie, regular lactose 19 calorie, low lactose 22 calorie, and regular lactose 22 calorie. The neonates that had the 22 calorie formula regardless of lactose concentration had a decreased length of hospital stay and shorter medication treatment when compared to neonates in the 19 calorie groups (Kaplan et al., 2017). The higher concentration formula is needed to meet the higher metabolic demands of a baby going through active withdrawal and helps to decrease the weight loss seen in babies diagnosed with NAS. The higher calorie formula is only needed for the first week of life during the initial withdrawal period (Walsh et al., 2018).

Box 30.1

NONPHARMACOLOGICAL INTERVENTIONS FOR NAS

Swaddling—in a flexed position with hands midline against chest and legs loosely swaddled in lumbar flexion to decrease sensory stimulation

Minimize environmental and physical stimulation—low lighting and noise levels—do not use TV or mobiles

Avoidance of abrupt changes in infant's environment—handling neonate gently and keeping neonate close to the body to increase sense of security

Skin-to-skin care with the mother or other family members

Gentle rocking—vertical rocking preferred over horizontal rocking

Slow approach with a soft voice and gentle touching to awaken baby and prepare for cares

Limit all stimulation at first signs of distress

Pacifiers for nonnutritive sucking

Hand containment during cares—involve the mother with this when she is present

Use of soft shushing, singing, or humming

Offer firm input to feet for bracing during feeds, your hand on the infant's chest to offer firm support and maintain flexion, which will increase organization for sucking, and apply firm pressure to palate to increase and improve quality of sucking

Frequent, small feedings for infants with feeding difficulties or gavage feeds may be needed

Avoid talking to the infant while feeding or rocking

Clustering care with extended rest periods

Encourage mother to room-in with neonate

Prone sleeping until stable, then transition to back sleeping for safe sleep at home

Relaxation baths

Acupuncture

Massage therapy

Aromatherapy using mother's scent

Pharmacological

When nonpharmacological treatments do not work, medication-assisted treatment will be needed to help alleviate the signs of withdrawal in the neonate. The recommendation of the AAP is to use the same medication class of the drug the neonate was exposed to in-utero (Kocherlakota, 2014). For narcotics and heroin, oral morphine and methadone are the most commonly used medications to help alleviate the withdrawal symptoms, though paregoric and tincture of opium continue to be used despite recommendations against these drugs. Several studies have been done comparing morphine to methadone for treatment in the neonate withdrawing from opiates, but to date there is no consensus on which one is better. One of the issues when looking at the studies is that there is no national standard on how to prescribe or when to start the medication therapy (Sanlorenzo, Stark, & Patrick, 2018). Buprenorphine, which is a mainstay in treating pregnant women with opiate-use disorder, has been recently studied in neonates as an alternative to morphine and methadone. In a small, single site, randomized double-blinded, double-dummy trial, buprenorphine was compared to morphine. The results of this study showed that buprenorphine-treated neonates had a significantly decreased length of hospital stay and a decreased length of treatment than neonates treated with morphine (Kraft et al., 2017).

For babies born to mothers who are polysubstance abusers with drugs such as barbiturates, benzodiazepines, antidepressants, and/or antipsychotics and sedatives or hypnotics, phenobarbital and clonidine can be used in conjunction with the narcotic replacement medications (Kocherlakota, 2014). Table 30.3 lists the most commonly used medications in NAS treatment with the route of administration and dosage.

No matter what pharmacological agent is used, the standardization of a medication protocol has been shown to be beneficial in decreasing the length of treatment and the hospital stay. The Ohio Children's Hospital Consortium from 2012 to 2014 did a multicenter retrospective cohort study with 981 neonates on the implementation of a standardized NAS weaning protocol. Prior to forming the consortium, each of the six children's hospitals treated NAS neonates in a different manner. Approximately halfway through the study, all the hospitals adopted a strict weaning protocol for either morphine or methadone. The adoption of the weaning protocol resulted in a shorter hospital stay, shorter duration

TABLE 30.3

COMMONLY USED MEDICATIONS TO CONTROL NEONATAL ABSTINENCE SYNDROME SYMPTOMS

Medication	Route	Dose Range
Morphine	PO	0.05–0.2 mg/kg/dose q3–4h; increase by 0.05 mg/kg Maximum dose: 1.3 mg/kg/day
Methadone	PO	0.05–0.1 mg/kg/dose q12h, increase by 0.05 mg/kg q48h Maximum dose: 1 mg/kg/day
Buprenorphine	Sublingual	4–5 mcg/kg/dose q8h Maximum dose: 60 mcg/kg/day
Phenobarbital	PO	Loading dose: 16 mg/kg Maintenance dose: 1–4 mg/kg/dose q12h
Clonidine	PO	Initial dose: 0.5–1 mcg/kg, followed by 0.5–1.25 mcg/kg/dose q4–6h

PO, by mouth.

Source: Adapted from Kocherlakota, P. (2014). Neonatal abstinence syndrome. *Pediatrics, 134*(2), e547–e561. doi:10.1542/peds.2013-3524

of opioid treatment, and less need for adjunct therapy in the three centers that did not previously have a protocol (Hall et al., 2015).

DEVELOPMENTAL OUTCOMES

While the acute signs of withdrawal can be ameliorated in days to weeks, subacute signs may last as long as 6 months, which can affect the development of the neonate (Hudak & Tan, 2012). Studies have been published and are currently being done on the long-term outcomes of neonates diagnosed with NAS, but the true effects are not totally known as it is difficult to determine the actual cause of developmental delays. Neonates diagnosed with NAS usually have had exposure to more than one substance in-utero and many are raised in unstable home environments, shifting from one caretaker to another. Confounding factors such as low socio-economic class, poor nutrition, lack of parenting skills due to use of multiple drugs and/or psychiatric issues, and poor prenatal care, to name a few, are known to affect the development of a neonate. Furthermore, apart from NAS, most neonates are healthy, so long-term follow-up is often difficult as the parents don't see the need for developmental follow-up of their child if they appear to be hitting their developmental milestones (Oei, 2018).

Outcomes explored in studies are the effects of chronic drug exposure in-utero on vision and motor function; cognitive function and neurodevelopment; risk of addiction; emotional, behavioral, and social adjustment; resilience; physical health; academic outcomes; and potential criminal activity in adulthood, but all of them are contaminated by multiple drug exposures and adverse lifestyles, all of which cannot be discussed in this chapter.

Recent studies have been published on visual disturbances being observed in neonates exposed to opiates. Visual disturbances range from strabismus, nystagmus, reduced visual acuity, refractive errors, and cerebral visual impairment (Hamilton et al., 2010; Spiteri-Cornish, Hrabovsky, Scott, Myerscough, & Reddy, 2013). These disturbances are being noticed in the preschool to kindergarten age group and at this point it is undetermined if this will continue as the child grows and develops.

For cognitive function and neurobehavioral function, a study on the effects of prenatal cannabis on adults was done in Canada. The study followed children until they were 22 years of age. Early concerns regarding behavioral issues had resolved by adulthood and the adults performed similarly to non–cannabis-exposed adults on cognitive testing. But a functional magnetic resonance imaging demonstrated significantly different blood flow response to the posterior left brain, a side effect of the prenatal exposure (Smith et al., 2016; World Health Organization, n.d.).

A study on opioid exposure demonstrated that those exposed had decreased cognitive and fine motor function when compared to non-exposed adults in both the early childhood period and adulthood. Again, confounding factors such as being in an adverse home situation with parents who lack parenting skills, poverty, and chaos at home affect developmental outcomes, which many of these subjects had been exposed to (Nygaard, Slinning, Moe, & Walhovd, 2017; Ornoy, 2001; Ornoy, Segal, Bar-Hamburger, & Greenbaum, 2001).

The risk of future addition problems is of concern for neonates exposed in-utero. It is now well-known that there is a genetic component to addiction as well as environmental factors. **Quality and Safety: When comparing children of parents without addiction problems to children of parents who are addicts, the latter is two times more likely to develop an addiction disorder to substances such as alcohol and/or drugs** (Chasin, Pitts, & DeLucia, 1999). A study on prenatal cannabis exposure demonstrated that the endo-cannabinoid system that modulates and influences neurodevelopment into adulthood is affected. This leads to an increased risk of poor social outcomes, criminal activity, higher failure rates in school, having children out of wedlock, unemployment, and psychiatric issues (Goldschmidt, Richardson, Cornelius, & Day, 2004; Leech, Larkby, Day, & Day, 2006; Sonon, Richardson, Cornelius, Kim, & Day, 2016).

NONJUDGMENTAL NURSING CARE OF THE MOTHER–INFANT DYAD

When caring for the baby diagnosed with NAS it is important to remember that you are not only caring for the neonate, but also for the mother. Unfortunately many healthcare providers view the mothers with substance abuse disorder through a judgmental lens. Frequent comments from healthcare providers are: "The mother shouldn't have gotten pregnant," "What a horrible thing she did to her baby!", "If she loved her baby she would have just quit," or "She should be put in jail for what she did to her baby." These statements or thoughts are often heard by the mother or she will feel the judgment of the provider by his or her actions and attitude. When caring for the mother–infant dyad it is important to remember that up to 40% or more of women with substance use disorder are victims of child abuse, sexual abuse, or both (Konkolÿ-Thege et al., 2017). So, it is important when caring for the mother–infant dyad that you confront your feelings about the fact that the infants were exposed to substances in-utero. Remind yourself that addiction is a chronic disease similar to diabetes and hypertension, and that the woman did not decide to have a substance use disorder after becoming pregnant. The mother of the NAS neonate deserves to be treated with the same respect as any patient's mother you care for. In order to deal with mothers with substance abuse disorder, seeking education on trauma-informed care will help to care for them and their infants without judgment.

Quality and Safety: Nursing care of the neonate requires doing careful ongoing physical assessments, always being mindful of any potential seizure activity. Documentation of the baby's tolerance to stimuli is important as is monitoring the baby's fluid and electrolyte balance and daily weights. When caring for a baby requiring medication-assisted treatment, it is important to give the medication as ordered and on time.

When caring for the baby, you will also be interacting with the mother, so it is essential that you develop a therapeutic relationship with the mother and show her respect. This will encourage the mother to be more open to teaching and interventions. The mother is part of the caregiving team and needs to be taught how to provide supportive care to her infant. You can help her bond with her baby by providing skin-to-skin care opportunities for the mother, encouraging her to room-in with her infant, and by providing positive feedback for all attempts to comfort her infant. Explaining to the mother that the infant's behavior is not a reflection of her but a result of the drugs the baby was exposed to in-utero, and intervening early when the infant is fussy, will also help her bond with her infant.

When providing information to the mothers, always provide clear, concise, and specific guidelines for expected behaviors. The education should be goal-directed and the educational materials need to be presented in a nonjudgmental manner and at an appropriate reading level.

Caring for infants diagnosed with NAS and their mothers can be a difficult and tiring assignment. It is important to acknowledge to yourself that the mothers and infants require flexibility in schedules, energy, patience, and a nonjudgmental attitude. While it is good to provide consistent caregivers for these mother–infant dyads, it is also important to take breaks in order to prevent burnout.

When the infant is ready for discharge, it is important to make the appropriate referrals, if not done prior to discharge. A home health referral should be made as well as a referral to an early intervention or Help Me Grow program. If the mom is not already in a drug rehabilitation program, then a referral to a program should be done as this is a period where treatment can be most successful.

SUMMARY

Maternal opiate addiction in the United States has become a national epidemic. NAS is a result of this epidemic and has increased in prevalence. Maternal substance abuse disorder and NAS is costing hospitals and the government millions of dollars each year in treatment costs. Improving the care of infants with NAS and decreasing the length of stay in the hospital are two of the main issues facing hospitals and healthcare providers today. This chapter has attempted to discuss the many issues related to NAS as we currently understand them. There are still many unanswered questions related to the care of the infant with NAS regarding the best treatment strategy, the long-term outcomes, as well as why some infants do not show signs of withdrawal, even though there is known exposure in-utero.

EVIDENCE-BASED PRACTICE BOX

In the past decade or so there has been a dramatic shift in thinking regarding breastfeeding recommendations for mothers taking methadone. Prior to 2001, the AAP only recommended breastfeeding for mothers on methadone doses of 20 mg/day or less, because methadone is a small molecular-sized drug that is water-soluble with a weak base, and drugs that meet these criteria are known to readily transfer into human milk (Kreek, 1979; Kreek et al., 1974). However, studies on methadone in human milk between the 1970s and the 1990s demonstrated that mothers on methadone doses greater than 20 mg/day had very little methadone transfer through human milk to the neonate (Geraghty, Graham, Logan, & Weiss, 1997; Kreek et al., 1974; Pond, Kreek, Tong, Raghunath, & Benowitz, 1985; Wojnar-Horton et al., 1997). The data from these studies convinced the AAP Committee on Drugs to change their recommendations. The dose restriction was removed and methadone at all doses is now considered safe for the neonate (Hudak & Tan, 2012).

Studies in the 2000s continued to demonstrate only low amounts of methadone transfer into human milk, with minimal amounts measured in neonate and infant plasma. Methadone given in the United States contains both *R* and *S*-methadone and both substances are metabolized at different rates. Bogen et al. (2011) examined the levels of *R* and *S*-methadone in human milk on days 1 to 6 in postpartum women ($n = 20$) who were taking between 40 and 200 mg/day of methadone. The study looked at *R* and *S*-methadone levels in the breast milk as well as maternal plasma levels. The breast milk and maternal plasma levels were drawn when methadone levels were highest, to estimate maximum infant plasma levels. The study showed that *R*-methadone is found in higher concentrations than *S*-methadone. However, estimated levels of *R* and *S*-methadone in infant plasma were relatively low, even at the highest maternal methadone dose.

Jansson, Choo, Velez, Harrow, et al. (2008) studied the amount of methadone in breast milk in the first month of life. The maternal participants ($n = 8$) had both foremilk and hindmilk collected as well as blood drawn to assess maternal plasma levels of methadone. Additionally, the neonates had blood and urine collected to assess methadone levels. The study found that in the neonatal period—the initial 28 days of life—the amount of methadone found in the breast milk was low and unrelated to the mother's methadone dose. Methadone concentration in the breast milk did increase over the period of the study (30 days), but this did not increase the level of methadone in the neonate's plasma.

In a similar study, Jansson, Choo, Velez, Lowe, and Huestis (2008) studied methadone in breast milk in long-term lactation up to 6 months postpartum. Four of the five mothers who were followed up to 6 months postpartum had levels of methadone in breast milk that remained low.

In the past 10 years, buprenorphine has become the drug of choice for treating pregnant women with substance abuse problems. Similar studies done with methadone to determine the amount of drug in the breast milk have now been done in mothers who are receiving buprenorphine. Ilett, Hackett, Gower, Doherty, and Hamilton (2012) studied the amount of buprenorphine and norbuprenorphine a breastfed infant would receive during maternal maintenance treatment. The authors found that the norbuprenorphine concentration in the breast milk was 1.94 mcg/kg/day with an absolute infant dose of 0.29 mcg/kg/day, which was approximately half of the buprenorphine concentration of 3.65 mcg/kg/day and absolute infant dose of 0.55 mcg/kg/day (Ilett et al., 2012). Both the buprenorphine doses and norbuprenorphine doses were considered low and unlikely to cause problems in infants (Ilett et al., 2012).

In another study by Lindemalm, Nydert, Svenson, Stahle, and Sarman (2009), infant urine as well as the breast milk, urine, and blood of mothers who received buprenorphine in a treatment program and breastfed their babies were examined. The authors found that the levels of buprenorphine and its active metabolite norbuprenorphine were low, at less than 1% (Lindemalm et al., 2009). Finally Gower et al. (2014) looked at the long-term effect of buprenorphine on the infant. The authors examined infants at 4 weeks of age who had received breast milk from their mothers who were in buprenorphine treatment programs and found that there were no adverse side effects to the infants up to 4 weeks postnatally (Gower et al., 2014). Like the studies on methadone, the amount of drug transferred from the mother to the infant is low, thus supporting the recommendation by the AAP, ACOG, and ABM for breastfeeding with buprenorphine or methadone usage in a treatment program.

References

Bogen, D. L., Perel, J. M., Helsel, J. C., Hanusa, B. H., Thompson, M., & Wisner, K. L. (2011). Estimated infant exposure to enantiomer-specific methadone levels in breastmilk. *Breastfeeding Medicine, 6*(6), 377–384. doi:10.1089/bfm.2010.0060

Geraghty, B., Graham, E. A., Logan, B., & Weiss, E. L. (1997). Methadone levels in breast milk. *Journal of Human Lactation, 13*(3), 227–230. doi:10.1177/089033449701300312

Gower, S., Bartu, A., Ilett, K. F., Doherty, D., McLaurin, R., & Hamilton, D. (2014). The wellbeing of infants exposed to buprenorphine via breast milk at 4 weeks of age. *Journal of Human Lactation, 30*(2), 217–223. doi:10.1177/0890334413517748

Hudak, M. L., & Tan, R. C. (2012). Neonatal drug withdrawal. *Pediatrics, 129*(2), e540–e560. doi:10.1542/peds.2011-3212

Ilett, K. F., Hackett, L. P., Gower, S., Doherty, D., & Hamilton, D. (2012). Estimated dose exposure of the neonate to buprenorphine and its metabolite norbuprenorphine via breast milk during

EVIDENCE-BASED PRACTICE BOX (*continued*)

maternal buprenorphine substitution treatment. *Breastfeeding Medicine, 7*(4), 269–274. doi:10.1089/bfm.2011.0096

Jansson, L. M., Choo, R., Velez, M. L., Harrow, C., Schroeder, J. R., Shakleya, D. M., & Huestis, M. A. (2008). Methadone maintenance and breastfeeding in the neonatal period. *Pediatrics, 121*(1), 106–114. doi:10.1542/peds.2007-1182

Jansson, L. M., Choo, R., Velez, M. L., Lowe, R., & Huestis, M. A. (2008). Methadone maintenance and long-term lactation. *Breastfeeding Medicine, 3*(1), 34–37. doi:10.1089/bfm.2007.0032

Kreek, M. J. (1979). Methadone disposition during the perinatal period in humans. *Pharmacology, Biochemistry and Behavior, 11*(Suppl.), 7–13.

Kreek, M. J., Schecter, A., Gutjahr, C. L., Bowen, D., Field, F., Queenan, J., & Merkatz, I. (1974). Analysis of methadone and other drugs in maternal and neonatal body fluids: Use in evaluation of symptoms in a neonate of mother maintained on methadone. *American Journal of Drug and Alcohol Abuse, 1*(3), 409–419. doi:10.3109/00952997409011033

Lindemalm, S., Nydert, P., Svenson, J.-O., Stahle, L., & Sarman, I. (2009). Transfer of buprenorphine into breast milk and calculation of infant drug dose. *Journal of Human Lactation, 25*(2), 199–205. doi:10.1177/0890334408328295

Pond, S. M., Kreek, M. J., Tong, T. C., Raghunath, J., & Benowitz, N. L. (1985). Altered methadone pharmacokinetics in methadone-maintained pregnant women. *Journal of Pharmacology and Experimental Therapeutics, 233*(1), 1–6. Retrieved from http://jpet.aspetjournals.org/content/233/1/1

Wojnar-Horton, R. E., Kristensen, J. H., Yapp, P., Ilett, K. F., Dusci, L. J., & Hackett, L. P. (1997). Methadone distribution and excretion into breast milk of clients in a methadone maintenance programme. *British Journal of Clinical Pharmacology, 44*(6), 543–547. doi:10.1046/j.1365-2125.1997.t01-1-00624.x

CASE STUDY

Identification of Problem. Baby girl Jones, a 1-day-old, is admitted to the NICU from an outside referring hospital for high pitched crying, increasing irritability, tremors/jitteriness, increased muscle tone, poor feeding, emesis, and tachypnea requiring O_2 per nasal cannula.

Assessment: History and Physical. The baby girl was born at 39 1/7 weeks gestation at 3.2 kg to a 28-year-old gravida 4 para 4 AB 0, hepatitis B and C and HIV negative Caucasian mother. The pregnancy was complicated by no prenatal care and a history of Graves' disease, with the mother not compliant with medication therapy, unknown Group B bacterial streptococcal status, and opiate use. The baby was born by spontaneous vaginal delivery with clear amniotic fluid. The baby was vigorous at birth with Apgar scores of 8 and 8 and no resuscitation required. The mother's blood type was unknown and the baby's blood type was A positive. The infant was taken to the newborn nursery for tachypnea and O_2 administration and to be observed for signs of withdrawal. The infant was bottle-fed but had emesis with each feed. The course at the referring hospital was unremarkable except for increasing tachypnea with retractions, increasing irritability, poor feeding with emesis, tremors/jitteriness, and the requirement for continued O_2.

On admission to the NICU, the infant was noted to be alert and well-hydrated. The infant was on a nasal cannula at 0.1 L/minute for tachypnea with O_2 saturation at 99%. Her vital signs were within normal limits with an axillary temperature of 98.5°F, a heart rate of 150 beats/minute, a respiratory rate of 55 breaths/minute, and blood pressure of 60/36 mmHg with a mean of 48 mmHg. Her weight on admission was noted to be 2.88 kg, a 10% loss in 1 day. Her examination was nonremarkable, except for increased muscle tone. Finnegan scoring on the infant revealed a score of 8.

Differential Diagnosis. Several conditions in the neonate can cause the symptoms described in this infant. The most common are hypoglycemia, hypocalcemia, hypomagnesium, neurological insult, sepsis, and NAS. With the mother's history of being noncompliant with medication for Graves' disease, neonatal Graves' disease must also be considered.

Diagnostic Tests. To determine the exact cause of the signs, a glucose, calcium, and a complete blood count (CBC) differential should be ordered as well as a T_4 and TSH. The collection of meconium could be obtained from any remaining meconium that the infant passes and sent for toxicology. A call to the referring hospital to inquire if they collect umbilical cords at birth can also be made. If the cord was saved, then sending the cord for toxicology should be ordered.

Working Diagnosis. The baby's CBC and differential were normal, the glucose was 60, and the calcium normal at 9.0. The T_4/TSH was normal at 2.3 and 3.14. The baby continued to be irritable and a poor feeder, with jitteriness and increased muscle tone, as well as tachypnea. The baby started to develop excoriation on her cheeks from frequent rubbing on the mattress. Urine toxicology returned from the referral hospital was positive for opiates. The working diagnosis for the infant is NAS secondary to in-utero exposure to opiates.

Development of Management Plan. The goal for the neonate with NAS is to alleviate signs of withdrawal through nonpharmacological and pharmacological management. Wean infant to room air (RA) from nasal cannula oxygen. Maintain O_2 saturation at 95% to 96%. Continue scoring the infant every 3 hours with the Finnegan Scoring Tool. Ensure the neonate is swaddled with hands midline and legs flexed and placed in a dark, quiet environment to decrease stimulation. Encourage the mother to do skin-to-skin care or to hold the baby as much as possible. Feed infant 22 calorie formula q3h, PO ad lib, since the mother is not yet in a treatment program. When the baby has three scores greater than 8 or two scores greater than 12, begin pharmacological therapy of morphine at 0.05 mg/kg q3h and increase as needed based on scores.

Implementation and Evaluation of Effectiveness. The infant was weaned to RA over the next 2 hours, maintaining O_2 saturation between 95% and 96%. Infant Finnegan scores began to escalate over the next 12 hours to three consecutive scores of 10, 12, and 14, respectively, despite maximizing nonpharmacological interventions. The infant was started on morphine at 0.05 mg/kg/dose PO at 36 hours of age. Symptoms continued to escalate and the dose was increased to 0.07 mg/kg/dose PO by 48 hours of age. On day of life (DOL) 4 the baby had been stable on the morphine dose for 48 hours with Finnegan scores less than 8 and weaning of the morphine began. By DOL 10, the infant had been weaned off the morphine but Finnegan scoring continued for an additional 48 hours to ensure that the infant did not start to display signs of withdrawal after the discontinuation of the morphine. The infant did not display any signs of withdrawal, so this was discontinued on DOL 12. The infant was discharged home on DOL 13 on full PO feeds of 19 calorie formula with a weight of 3.2 kg. The infant was discharged to the care of a foster family and, after completing all discharge, newborn testing and education was completed with the foster family. A referral was made to Help Me Grow and the NAS clinic at the regional referral center.

QUALITY AND SAFETY

Scoring

All NAS scores have a degree of subjectivity to them, making interrater reliability among staff of utmost importance when caring for neonates with NAS. Inconsistency in scoring from one nurse to another makes it difficult for the practitioner to manage the patient. Doing dual scoring at least two times per day helps to increase interrater reliability between nurses and increases confidence in the practitioners that the neonate is actually scoring the number that has been assigned.

Pharmacological Treatment

When multiple practitioners care for a neonate with NAS, differences in management of the patient is a common occurrence. Practice differences in administering either morphine or methadone, as well as when and how to wean the neonate, can lead to increased days on medication therapy and in the hospital. Establishing a medication protocol that all practitioners can agree on, and adhering to the protocol, has been shown to improve outcomes by decreasing the length of time on medication and the number of days in the hospital.

General Management of NAS Patients

Quality improvement is now part of all NICUs and SCNs. NAS babies can have long length of stays. A quality improvement project to decrease the length of stays has been shown to work. A multidisciplinary team will be needed to develop a specific aim, determining key drivers that affect the aim and then designing interventions to achieve the aim through a series of Plan-Do-Study-Act cycles. When creating your team, be sure to include a former patient mother to help, as parents have many great ideas on what can and cannot work!

Breastfeeding NAS Babies

One of the many reasons for poor breastfeeding rates in mothers of babies diagnosed with NAS is the fear by healthcare providers that substances will transfer into the maternal breast milk, thus harming the baby. This fear by the healthcare provider is usually due to a lack of understanding of the pharmacokinetics of medications in breast milk. An education program to increase the healthcare knowledge on the subject can help increase breastfeeding as the providers are more likely to assist and support the breastfeeding mother.

ONLINE RESOURCES

Academy of Neonatal Nursing. (n.d.). NAS resource center. Retrieved from https://www.academyonline.org/general/custom.asp?page=NAS

American Academy of Pediatrics. (2016). Clinical Report: Neonatal Drug Withdrawal. Retrieved from https://pediatrics.aappublications.org/content/137/5/e20160592

American College of Obstetricians and Gynecologists Committee on Obstetric Practice & American Society of Addition Medicine. (2017). Opioid use and opioid use disorder in pregnancy (Committee opinion no. 711). Retrieved from https://www.acog.org/-/media/Committee-Opinions/Committee-on-Obstetric-Practice/co711.pdf

Association of State and Territorial Health Officials. (n.d.). Neonatal abstinence syndrome. Retrieved from http://www.astho.org/Prevention/Rx/NAS

March of Dimes. (n.d.). Neonatal abstinence syndrome (NAS). Retrieved from https://www.marchofdimes.org/neonatal-abstinence-syndrome-(nas).aspx

National Association of Neonatal Nurses. (2018). Neonatal abstinence syndrome. Retrieved from http://babystepstohome.com/diagnoses/neonatal-abstinence-syndrome.pdf

National Association of State Alcohol and Drug Abuse Directors. (n.d.). Neonatal abstinence syndrome (Fact sheet). Retrieved from http://nasadad.wpengine.com/wp-content/uploads/2015/06/NAS-Fact-Sheet-Final.pdf

National Library of Medicine. (n.d.). Neonatal abstinence syndrome. Retrieved from https://medlineplus.gov/ency/article/007313.htm

Ohio Perinatal Quality Collaborative. Retrieved from https://opqc.net/projects/NAS

Tennessee Initiative for Perinatal Quality Care. Retrieved from https://tipqc.org

REFERENCES

American College of Obstetricians and Gynecologists. (2017). Committee opinion no. 711 summary: Opioid use and opioid use disorder in pregnancy. *Obstetrics and Gynecology, 130*(2), 488–489. doi:10.1097/AOG.0000000000002229

Bagley, S. M., Wachman, E. M., Holland, E., & Brogly, S. B. (2014). Review of the assessment and management of neonatal abstinence syndrome. *Addiction Science and Clinical Practice, 9*(1), 19. doi:10.1186/1940-0640-9-19

Center for Behavioral Health Statistics and Quality. (2016). *Key substance use and mental health indicators in the United States: Results from the 2015 National Survey on Drug Use and Health* (HHS Publication No. SMA 16-4984, NSDUH Series H-51). Retrieved from http://www.samsha.gov/data

Chantry, C. J., Eglash, A., & Labbok, M. (2015). ABM position on breastfeeding–Revised 2015. *Breastfeeding Medicine, 10*(9), 407–411. doi:10.1089/bfm.2015.29012.cha

Charles, M. K., Cooper, W. O., Jansson, L. M., Dudley, J., Slaughter, J. C., & Patrick, S. W. (2017). Male sex associated with increased risk of neonatal abstinence syndrome. *Hospital Pediatrics, 7*(6), 1–7. doi:10.1542/hpeds.2016-0218

Chasin, L., Pitts, S. C., & DeLucia, C. (1999). The relation of adolescent substance use to young adult autonomy, positive activity involvement and perceived competence. *Development and Psychopathology, 11*(4), 915–932. doi:10.1017/S0954579499002382

Courtwright, D. T. (2001). *Dark paradise: A history of opiate addiction in America* (Rev. ed.). Cambridge, MA: Harvard University Press.

Finnegan, L. P., Cron, R. E., Connaughton, J. F., & Emich, J. P. (1975). Assessment and treatment of abstinence in the infant of the drug-dependent mother. *International Journal of Clinical Pharmacology and Biopharmacy, 12*(1/2), 19–32.

Finnegan, L. P., & MacNew, B. A. (1974). Care of the addicted infant. *American Journal of Nursing, 74*(4), 685–693. doi:10.2307/3469763

Goldschmidt, L., Richardson, G. A., Cornelius, M. D., & Day, N. L. (2004). Prenatal marijuana and alcohol exposure and academic achievement at age 10. *Neurotoxicology and Tetralogy, 26,* 521–532. doi:10.1016/j.ntt.2004.04.003

Gomez-Pomar, E., & Finnegan, L. P. (2018). The epidemic of neonatal abstinence syndrome, historical references of its origins, assessment and management. *Frontiers in Pediatrics, 6*(33), 1–8. doi:10.3389/fped.2018.00033

Gomez-Pomar, E., Finnegan, L. P., Devlin, L., Bada, H., Concina, V. A., Ibonia, K. T., & Westgate, P. M. (2017). Simplification of the Finnegan neonatal abstinence scoring system: Retrospective study of two institutions in the USA. *British Medical Journal, 7*(9), e016176. doi:10.1136/bmjopen-2017-016176

Green, M., & Suffett, F. (1981). The neonatal narcotic withdrawal index: A device for the improvement of care in the abstinence syndrome.

American Journal of Drug and Alcohol Abuse, 8(2), 203–213. doi:10.3109/00952998108999125

Hall, E. S., Wexelblatt, S. L., Crowley, M., Grow, J. L., Jasin, L. R., Klebanoff, M. A., . . . Walsh, M. C. (2014). A multicenter cohort study of treatments and hospital outcomes in neonatal abstinence syndrome. *Pediatrics, 134*(2), e527–e534. doi:10.1542/peds.2013-4036

Hall, E. S., Wexelblatt, S. L., Crowley, M., Grow, J. L., Jasin, L. R., Klebanoff, M. A., . . . Walsh, M. C.(2015). Implementation of a neonatal abstinence syndrome weaning protocol: A cohort study. *Pediatrics, 136*(4), e803–e810. doi:10.1542/peds.2015-1141

Hamilton, R., McGlone, I., MacKinnon, J. R., Russell, H. C., Bradnam, M. S., & Mactier, H. (2010). Ophthalmic, clinical and visual electrophysiological findings in children born to mothers prescribed methadone in pregnancy. *British Journal of Ophthalmology, 94*(6), 696–700. doi:10.1136/bjo.2009.169284

Hudak, M. L., & Tan, R. C. (2012). Neonatal drug withdrawal. *Pediatrics, 129*(2), e540–e560. doi:10.1542/peds.2011-3212

Huybrechts, K. F., Bateman, B. T., Desai, R. J., Hernandez-Diaz, S., Rough, K., Mogun, H., . . . , Patorno, E. (2017). Risk of neonatal drug withdrawal after intrauterine co-exposure to opioids and psychotropic medications: Cohort study. *British Medical Journal, 358*, :j3326. doi:10.1136/bmj.j3326

Jansson, L. M., Choo, R., Velez, M. L., Lowe, R., & Huestis, M. A. (2008). Methadone maintenance and long-term lactation. *Breastfeeding Medicine, 3*(1), 34–37. doi:10.1089/bfm.2007.0032

Jansson, L. M., Velez, M. L., & Butz, A. M. (2017). The effect of sexual abuse and prenatal substance use on successful breastfeeding. *Journal of Obstetrics, Gynecology and Neonatal Nursing, 46*(3), 480–484. doi:10.106/jogn.2017.002

Jones, H. E., Kaltenbach, K., Heil, S. H., Stine, S. M., Coyle, M. G., Arria, A. M., . . . Fischer, G. (2010). Neonatal abstinence syndrome after methadone or buprenorphine exposure. *New England Journal of Medicine, 363*(24), 2320–2331. doi:10.1056/NEJMoa1005359

Kaplan H., Kuhnell, P., Macaluso, M., Ford, S., Crowley, M,. McClead, R., . . . Walsh, M. (2017). Quality Improvement with Orchestrated Testing to Identify Best Formula Feeding for Neonatal Abstinence Syndrome (NAS). Poster session presented at: Pediatric Academic Societies 2017 Meeting; 2017 May 6–9; San Francisco, CA.

Kocherlakota, P. (2014). Neonatal abstinence syndrome. *Pediatrics, 134*(2), e547–e561. doi:10.1542/peds.2013-3524

Konkolÿ-Thege, B., Horwood, L., Slater, L., Tan, M. C., Hodgins, D. C., & Wild, T. C. (2017). Relationship between interpersonal trauma exposure and addictive behaviors: A systematic review. *British Medical Journal Psychiatry, 17*(1), 164. doi:10.1186/s12888-017-1323-1

Kraft, W. K., Adeniyi-Jones, S. C., Chervoneva, I., Greenspan, J. S., Abatemarco, D., Kaltenbach, K., & Ehrlich, M. E. (2017). Buprenorphine for the treatment of neonatal abstinence syndrome. *New England Journal of Medicine, 376*(24), 2341–2348. doi:10.1056/NEJMoa1614835

Kwong, T. C., & Ryan, R. M. (1997). Detection of intrauterine illicit drug exposure by newborn drug testing. *Clinical Chemistry, 43*(1), 235–242. Retrieved from http://clinchem.aaccjnls.org/content/clinchem/43/1/235.full.pdf

Leech, S. L., Larkby, C. A., Day, R., & Day, N. L. (2006). Predictors and correlates of high levels of depression and anxiety symptoms among children at age 10. *Journal of American Academy of Child and Adolescent Psychiatry, 45*(2), 223–230. doi:10.1097/01.chi.0000184930.18552.4d

Lipsitz, P. J. (1975). A proposed narcotic withdrawal score for use with newborn infants. A pragmatic evaluation of its efficacy. *Clinical Pediatrics, 14*(6), 592–594. doi:10.1177/000992287501400613

Liu, A. J., Jones, M. P., Murray, H., Cook, C. M., & Nanan, R. (2010). Perinatal risk factors for the neonatal abstinence syndrome in infants born to women on methadone maintenance therapy. *Australian New Zealand Journal of Obstetrics and Gynecology, 50*(3), 253–258. doi:10.1111/j.1479-828x.2010.01168.x

Mactier, H., McLaughlin, P., Gillis, C., & Osseton, M. D. (2017). Variations in infant CYP2B6 genotype associated with the need for pharmacological treatment for neonatal abstinence syndrome in infants of methadone-maintained opioid dependent mothers. *American Journal of Perinatology, 34*(9), 918–921. doi:10.1055/s-0037-1600917

Maguire, D., Cline, G. J., Parnell, L., & Tai, C.-Y. (2013). Validation of the Finnegan neonatal abstinence syndrome tool-short form. *Advances in Neonatal Care, 13*(6), 430–437. doi:10.1097/ANC.0000000000000033

McQueen, K. A., Murphy-Oikonen, J., Gerlach, K., & Montelpare, W. (2011). The impact of infant feeding method on neonatal abstinence scores of methadone-exposed infants. *Advances in Neonatal Care, 11*(4), 282–290. doi:10.1097/ANC.0b013e318225a30c

National Institute on Drug Abuse. (2018). *Screening and assessment tools chart*. Retrieved from https://www.drugabuse.gov/nidamed-medical-health-professionals/tool-resources-your-practice/screening-assessment-drug-testing-resources/chart-evidence-based-screening-tools-adults

Nygaard, E. Slinning, K., Moe, V., & Walhovd, K. B. (2017). Cognitive function of youths born to mothers with opioid and poly-substance abuse problems during pregnancy. *Child Neuropsychology, 23*(2), 159–187. doi:10.1080/09297049.2015.1092509

Oei, J. L. (2018). Adult consequences of prenatal drug exposure. *Internal Medicine Journal, 48*(1), 25–31. doi:10.1111/imj.13658

Ornoy, A. (2003). The impact of intrauterine exposure versus postnatal environment in neurodevelopmental toxicity: Long-term neurobehavioral studies in children at risk for developmental disorders. *Toxicology Letters, 140–141*, 171–181. doi:10.1016/s0378-4274(02)00505-2

Ornoy, A., Segal, J., Bar-Hamburger, R., & Greenbaum, C. (2001). Developmental outcome of school age children born to mothers with heroin dependency: Importance of environmental factors. *Developmental Medicine and Child Neurology, 43*(10), 668–675. doi:10.1111/j.1469-8749.2001.tb00140.x

Ostrea, E. M., Jr., Chavez, C. J., Strauss, M. E. (1976) A study of factors that influence the severity of neonatal narcotic withdrawal. *Journal of Pediatarics*, *88*(4), 642–645. doi: 10.1016/S0022-3476(76)80027-3

Patrick, S. W., Davis, M. M., Lehmann, C. U., & Cooper, W. O. (2015). Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009-2012. *Journal of Perinatology, 35*(8), 650–655. doi:10.1038/jp.2015.36

Patrick, S. W., Schumacher, R. E., Benneyworth, B. D., Krans, E. E., McAllister, J. M., & Davis, M. M. (2012). Neonatal abstinence syndrome and associated healthcare expenditures: United States 2000-2009. *Journal of American Medical Association, 307*(18), 1934–1940. doi:10.1001/jama.2012.3951

Perlstein, M. A. (1947). Congenital morphinism: A rare cause of convulsions in the newborn. *Journal of the American Medical Association, 135*(10), 633. doi:10.1001/jama.1947.62890100006006c

Pritham, U. A., Paul, J. A., & Hayes, M. J. (2012). Opioid dependency in pregnancy and length of stay for neonatal abstinence syndrome. *Journal of Obstetrics, Gynecology, and Neonatal Nursing, 41*(2), 180–190. doi:10.1111/j.1552-6909.2011.01330.x

Quinones, S. (2015). *Dreamland: The true tale of America's opiate epidemic*. New York, NY: Bloomsbury Press.

Sanlorenzo, L. A., Stark, A. R., & Patrick, S. W. (2018). Neonatal abstinence syndrome: An update. *Current Opinion in Pediatrics, 30*(2), 182–186. doi:10.1097/MOP.0000000000000589

Short, V. L., Gannon, M., & Abatemarco, D. J. (2016). Association between breastfeeding and length of hospital stay among infants diagnosed with neonatal abstinence syndrome: A population-based study of in-hospital births. *Breastfeeding Medicine, 11*(7), 343–349. doi:10.1089.bfm.2016.0084

Smith, A. M., Mioduszewski, O., Hatchard, T., Byron-Alhassan, A., Fall, C., & Fried, P. A. (2016). Prenatal marijuana exposure impacts executive functioning into young adulthood: An fMRI study. *Neurotoxicology and Teratology, 58, 53–59*. doi:10.1016/j.ntt.2016.05.010

Sonon, K., Richardson, G. A., Cornelius, J., Kim, K. H., & Day, N. L. (2016). Developmental pathways from prenatal marijuana exposure to cannabis use disorder in young adulthood. *Neurotoxicology and Tetralogy, 58*, 46–52. doi:10.1016/j.ntt.2016.05.004

Spiteri-Cornish, K., Hrabovsky, M., Scott, N.W., Myerscough, E. & Reddy, A.R. (2013). The short- and long-term effects on the visual system of children following exposure to maternal substance misuse in pregnancy. *American Journal of Opthalmology, 156*(1), 190–194. doi:10.1016/j.apo.2013.02.004

Substance Abuse and Mental Health Services Administration-Health Resources and Services Administration Center for Integrated Health Solutions. (n.d). Motivational interviewing. Retrieved from http://www.integration.samhsa.gov/clinical-practice/motivational-interviewing

Sutter, M. B., Leeman, L., & Hsi, A. (2014). Neonatal opioid withdrawal syndrome. *Obstetrics and Gynecology Clinics of North America, 41*(2), 317–334. doi:10.1016/j.ogc.2014.02.010

Tolia, V. N., Patrick, S. W., Bennett, M. M., Murphy, K., Sousa, J., Smith, P. B., . . . Spitzer, A. R. (2015). Increasing incidence of the neonatal abstinence syndrome in U. S. neonatal ICU's. *New England Journal of Medicine, 372*(22), 2118–2126. doi:10.1056/NEJMsa1500439

United States Drug Testing Laboratories. (n.d.). Frequently asked questions. Retrieved from http://www.usdtl.com/faq

Vinner, E., Vignau, J., Thibault, D., Codaccioni, X., Brassart, C., Humbert, L., & Lhermitte, M. (2003). Neonatal hair analysis contribution to establishing a gestational drug exposure profile and predicting a withdrawal syndrome. *Therapeutic Drug Monitoring, 25*(4), 421–432. doi:10.1097/00007691-200308000-00002

Wachman, E. M., Byun, J., & Philipp, B. L. (2010). Breastfeeding rates among mothers of infants with neonatal abstinence syndrome. *Breastfeeding Medicine, 5*(4), 159–164. doi:10.1089/bfm.2009.0079

Wachman, E. M., Hayes, M. J., & Brown, M. S. (2013). Association of OPRM1 and COMT single-nucleotide polymorphisms with hospital length of stay and treatment of neonatal abstinence syndrome. *Journal of American Medical Association, 309*(17), 1821–1827. doi:10.1001/jama.2013.3411

Wachman, E. M., Schiff, D. M., & Silverstein, M. (2018). Neonatal abstinence syndrome: Advances in diagnosis and treatment. *Journal of American Medical Association, 319*(13), 1362–1374. doi:10.1001/jama.2018.2640

Walsh, M. C., Crowley, M., Wexelblatt, S., Ford, S., Kuhnell, P., Kaplan, H. C., . . . Lannon, C. (2018). Ohio Perinatal Quality Collaborative improves care of neonatal narcotic abstinence syndrome. *Pediatrics, 141*(4), e20170900. doi:10.1542/peds.2017-0900

Winkelman, T. N. A., Villapiano, N., Kozhimannil, K. B., Davis, M. M., & Patrick, S. W. (2018). Incidence and costs of neonatal abstinence syndrome among infants with Medicaid: 2004-2014. *Pediatrics, 141*(4), e20173520. doi:10.1052/peds.2017-3520

World Health Organization. (n.d.). Cannabis. Retrieved from http://www.who.int/substance_abuse/facts/cannabis/en

Zahorodny, W., Rom, C., Whitney, W., Giddens, S., Samuel, M., Maichuk, G., & Marshall, R. (1998). The neonatal withdrawal inventory: A simplified score of newborn withdrawal. *Journal of Developmental and Behavioral Pediatrics, 19*(2), 89–93. doi:10.1097/00004703-199804000-00005

Unit VI: Environmental Health and Family-Centered Care in the NICU and Beyond

CHAPTER 31

Neurobehavioral Development

Leslie B. Altimier and Diane Holditch-Davis

INTRODUCTION

The care of high-risk infants, both those born prematurely and those with medical, surgical, or developmental problems, has long been a major focus of nursing and healthcare. Advances in neonatal care have increasingly focused on the impact of the neonatal intensive care unit (NICU) environment on the infant's physiologic and neurobehavioral functioning, the provision of sensory input geared to meet the individual infant's needs and current level of developmental function, and mediating the effects of stress and overstimulation. Care in the NICU focuses on meeting the physiologic, neurobehavioral, and developmental needs of these infants, with attention to the social interactive consequences of the NICU environment. This chapter focuses on the improved understanding of these factors and of the pathophysiologic problems encountered by infants in the NICU, along with the development of new management strategies, technologies, and caregiving approaches that have markedly improved the outcome of high-risk infants.

CONSEQUENCES OF PREMATURITY

Birth at extremely low gestational ages presents a significant threat to an infant's survival, health, development, and future well-being. Although comprising just 1% to 2% of all births, extremely preterm infants (delivered at 22–28 weeks' gestation) pose the greatest challenge to neonatal medicine, healthcare, education, and social services in providing continued support for survivors who often have significant ongoing needs. Among infants born at 22, 23, and 24 weeks, survival to 1 year of age was 6%, 27%, and 60%, respectively, and increased for each 1-week increase in gestational age (GA) from 78% at 25 weeks to 94% at 28 weeks (Anderson et al., 2016). Survival depends highly on the place of birth. Hospitals with larger neonatal services and more experience in the care of extremely low birth weight (ELBW, <1,000 g birth weight) infants have higher rates of survival (Marlow et al., 2014). The prevalence of major neonatal morbidities common to this gestational age group—chronic lung disease (CLD) or bronchopulmonary dysplasia (BPD), periventricular leukomalacia (PVL), intraventricular hemorrhage (IVH), cerebral palsy (CP), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), severe visual and hearing impairment, and sepsis—is essentially unchanged, despite continually evolving less invasive strategies (Costeloe, Hennessy, Haider, Stacey, & Marlow, 2012).

Premature infants also remain at high risk for a variety of neurodevelopmental, cognitive, behavioral, motoric, visual, hearing, attentional, social, emotional, and educational problems (Adam-Chapman et al., 2018; Anderson et al., 2016; Ditzenberger, Blackburn, Brown, & Altimier, 2016; Marlow et al., 2014; Moore et al., 2018; Neil & Inder, 2018; Symes, 2016). Infants born very preterm (before 32 weeks' GA) are three times more likely than full-term born infants to develop psychiatric disorders (Johnson & Marlow, 2011), and are at higher risk for a wide range of sociocognitive impairments (Blencowe et al., 2013; Spittle, 2016; Synnes & Hicks, 2018).

It is well documented that parents of NICU babies have significantly higher rates of postpartum depression (PPD), posttraumatic stress disorder (PTSD), and anxiety disorders (M. M. Greene et al., 2015). The psychosocial needs of parents who are enduring the unexpected and extreme stress of having a hospitalized preterm or sick newborn have been long neglected, and most NICU staff (medical, nursing, and therapy) have not been trained to recognize the psychosocial needs of NICU parents. While much support can readily be given by compassionate, caring, trained NICU staff, some parents will require referral to mental health professionals. Since neurodevelopment outcomes of NICU babies are directly linked to secure attachments with their parents, supporting NICU parents in developing bonds of attachment with their babies can be considered neuroprotective care (Altimier & Phillips, 2018).

Although survival rates for ELBW premature infants have improved, there has only been a modest improvement in the proportion of surviving infants without neurologic impairment, no change in the proportion with severe disability, and an overall increase in the total number of children with neurodisability (Anderson, 2018; Holsti, Serenius, & Farooqi, 2018). Infants born at 25 weeks' GA have predicted survival rates exceeding 70%; however, along with improved survival rates, the risk of neurodevelopmental impairment increases with the degree of prematurity, reaching rates as high as 80% at 23 weeks' GA (Glass et al., 2015).

Executive functions, a set of inter-related cognitive processes that allow individuals to respond flexibly to the environment and to engage in purposeful, goal-directed behavior, often include,

but are not limited to, inhibition, planning, shifting or cognitive flexibility, working memory, and verbal fluency (Anderson, 2014; Burnett, Cheong, & Doyle, 2018; Farooqi, Hägglöf, Sedin, & Serenius, 2011; Samuelsson et al., 2017). Deficits in these executive functions have been reported in very preterm and very low birthweight (VLBW, <1,500 g birth weight) infants, with a greater deficit noted in infants born less than 26 weeks' gestation, which appear to persist over time into adolescence (Burnett et al., 2018; Holsti et al., 2018).

Authors have reported that 21% to 41% of extremely preterm children screen positive for the risk for autism spectrum disorders (ASD) at 2 years corrected age (Agrawal, Rao, Bulsara, & Patole, 2018). It is also thought that these may be core cognitive deficits that underlie much of the psychiatric morbidity and learning difficulties in this population (Patra & Greene, 2018).

Healthcare utilization is extremely high among preterm infants in recent years and significantly associated with worse neurodevelopmental outcomes (Patra & Greene, 2018). Prematurity of any degree affects the cognitive performance of children born preterm and the poor neurodevelopment persists at various ages of follow-up (Allotey et al., 2018).

Extremely preterm children are less likely to complete basic school education and are more likely to have poorer academic attainment than both their term-born peers and their more mature preterm counterparts. They also experience significantly increased rates of learning difficulties. Consequently, 39% to 62% of extremely preterm children are reported to have special educational needs (ElHassan et al., 2018; Litt et al., 2012); therefore, it is not surprising that after care in the NICU, the greatest costs associated with support for extremely preterm children lie in education (Dmowska, Andrews, Schreiber, & Msall, 2016; Hall & Greenberg, 2016; Mangham, Petrou, Doyle, Draper, & Marlow, 2009; Petrou, Johnson, Wolke, & Marlow, 2013). An innovative methodology to calculate community-level costs associated with preterm birth was performed by Hall and Greenberg (2016). Costs included initial direct hospital expenditures from the perspective of delivery hospitals and insurers, as well as indirect costs incurred through decreased educational attainment and lost earnings from the perspective of adults who were born preterm. The total initial hospital cost for all births within each GA category was calculated. Maternal costs were calculated a single time for each singleton delivery or set of gestation deliveries. To determine the excess cost attributed to prematurity, the initial hospital costs of full-term care for an equivalent number of infants were subtracted from the totals. Next, cost savings were calculated, which could be potentially realized by prolonging each preterm pregnancy by a single week of gestation.

Next, the impact of preterm birth on local educational attainment and annual income using measures obtained from the American Communities Survey (ACS) were estimated. An adjusted number of degrees that would have been expected had the preterm population earned degrees in the same proportion as the full-term population were then calculated (estimating the difference between earned degrees and adjusted degrees as the number of "lost" degrees attributable to preterm birth). Next, the impact of preterm birth on earnings (mean annual incomes associated with three income levels) among working adults was calculated.

Then, an adjusted income that would have been expected had the preterm population earned income in the same proportion as the full-term population was calculated (estimating the difference between actual earnings and adjusted earnings as "lost" earnings attributable to preterm birth). Lastly, the difference in both lost degrees and lost earnings if the rate of adults who were born preterm shifted from 10% to 9% was calculated. The preterm population represented 13.2% of the population, but 74.1% of the $131.7 million total initial hospital costs.

The annual initial hospital cost associated with 1,444 preterm infants was estimated at $93 million. In addition, over 9,000 fewer college degrees and over $300 million in lost annual earnings were attributed to local adults who were born preterm. Prolonging each preterm birth by 1 week could potentially reduce initial hospital expenditures by over $25 million. Additional potential savings could be realized as healthier infants attain higher levels of education and earnings as adults. The generalizable methods developed for estimating the economic impact of preterm birth at the community level can serve to rally support for local stakeholder investments in developing strategies for preterm birth intervention leading to improved pregnancy outcomes (Hall & Greenberg, 2016).

Immature infants differ in two important ways from healthy full-term infants. First, these infants are born early and therefore must adapt to the extrauterine environment with bodily systems, including a central nervous system (CNS), that are not yet mature. Second, this interruption of intrauterine life significantly modifies the environment of the infant. Thus, the preterm infant spends the last weeks or months of gestation in an environment—the NICU—that is very different from that of the uterus or the home of a healthy full-term infant. The NICU environment has similar implications for the more mature, although still vulnerable, ill full-term infant. For these infants, this environment is also abnormal and quite different from that experienced by healthy infants who go home with their parents soon after birth.

Neonatal nurses are very familiar with interpreting the physiologic status of infants and basing their interventions on physiologic changes. In recent years, nurses have placed increased emphasis on the importance of understanding the behaviors of infants under their care because behavior is the way infants communicate their needs and their responses to nursing interventions. However, two factors make this understanding difficult. First, newborn infants have limited behavioral repertoires. The same behavior may have different meanings in different situations, but busy neonatal nurses may not have the time necessary to correctly interpret infants' behaviors by comprehensively assessing both the infants' actions and the environmental stimulation. Second, the behaviors of critically ill infants are sometimes even more difficult to interpret, because they lack the energy to display characteristic behavioral responses. Thus, neonatal nurses can never rely totally on infants' behaviors to determine their needs, but in combination with physiologic parameters, understanding infant behavior enriches both nursing assessment and the evaluation of nursing interventions. In considering the vulnerabilities of ill and immature infants, it is useful to examine the implications of the state of CNS and sensory system development, neonatal neurobehavioral development, and sleeping and waking states—and their relevance for neonatal nursing.

FETAL AND NEONATAL CENTRAL NERVOUS SYSTEM DEVELOPMENT

The brain grows and develops most rapidly during the fetal period and the first years of life. Total brain volume measured 2 to 4 weeks after birth is approximately 36% of that of an average adult brain. The brain increases in size by 101% during the first year and by another 15% during the second year, reaching over 80% of adult brain volume. During this rapid development, multiple interacting mechanisms such as myelination of white matter (WM) and functional specialization of brain areas is happening simultaneously (Dubois, Dehaene-Lambertz, Kulikova, Poupon, & Hu, 2014).

As noted in Chapter 15, Neurologic System, the development of the CNS can be divided into six overlapping stages (Table 15.1). These stages are important to consider in examining neurobehavioral development and the effects of the NICU environment, because the stage of development influences the effect of any insult. In addition, several areas of the CNS, including predominantly organizational processes, continue to undergo significant changes during the period when preterm infants are in the NICU, increasing their vulnerability to insult. Vulnerabilities include decreased inhibitory potential, slower nerve conduction and synaptic potential, inability to sustain high firing rates, incomplete cell differentiation, and decreased synaptogenesis and dendritic arborization. The stage of development is also reflected by the behavioral characteristic of immature infants such as altered state regulation, increased and decreased tone, alterations in primitive reflexes, increased irritability, immature inhibition, jerky movements, lower arousal, lesser ability to sustain alert states, poorer coordination, altered autonomic regulation, and asymmetrical, uncoordinated posture and movement (Blackburn, 2018; du Plessis & Volpe, 2018; Gressens & Huppi, 2015; K. L. Moore, Persaud, & Torchia, 2015; Yuskaitis & Pomeroy, 2017).

The first three stages of CNS development (dorsal induction, ventral induction, and neuronogenesis) are completed before the fourth month of gestation. The last three stages (neuron migration; organization, including synaptogenesis and arborization; and myelination) continue during the time many infants are in the NICU and have implications for the effects of the NICU environment and care. Areas of development during the last part of gestation that are particularly critical in considering neurobehavioral vulnerabilities of ill or immature infants include (1) autonomic homeostatic control, (2) alterations in the germinal matrix and migration of neurons and glial cells, (3) CNS organizational processes, (4) development of the neocortex, and (5) growth of the cortex and cerebellum (Blackburn, 2018; du Plessis & Volpe, 2018).

From about 28 to 32 weeks' GA, preterm infants begin to achieve some degree of physiologic homeostasis, with increasing control of the sympathetic system over their autonomic functioning. With increasing autonomic control, the infant develops greater autonomic stability. This autonomic stability can be seen, for example, in the decreasing incidence of apnea and bradycardia. As these infants move to greater cortical control over the next months, their development is characterized by periods of temporary organization followed by periods of disorganization as new levels of maturation and control are achieved. These periods of disorganization are reflected in the infant's sleep–wake patterns, proportion of transitional or indeterminate sleep, and fragmented behavioral responses, and reflexes (Moore et al., 2015).

The germinal matrix in the periventricular subependymal area is a site of origin for neuronal and glial cells. Neurons and glial cells migrate from the germinal matrix to their eventual loci within the CNS, where they further differentiate and take on unique and individual functions. Initially, the neurons migrate to areas deep within the cortex; later, neurons migrate further toward the surface of the cortex. Thus, neurons formed early come to lie in deeper layers of cortex and subcortex; those formed later are found in more superficial layers. The cortex generally has a complete component of neurons by 33 weeks' gestation (Yuskaitis & Pomeroy, 2017). Until 32 to 34 weeks' GA, the fragile, poorly supported blood vessels in this area receive a significant proportion of cerebral blood flow (du Plessis & Volpe, 2018). Insults to this area before this period may lead to germinal matrix and IVH (Blackburn, 2018; Fleiss, Mezger, & Gressens, 2018; Juul, Fleiss, McAdams, & Gressens, 2018; Poduri & Volpe, 2018a).

Organization, or "the processes by which the nervous system takes on the capacity to operate as an integrated whole," begins during the sixth month of gestation and extends many years after birth (Blackburn, 2018). Neuron growth and connections lead to development of brain sulci and gyri. A brain growth spurt occurs from 26 to 30 weeks, leading to more complex behaviors (Blackburn, 2018; du Plessis & Volpe, 2018). Organization of the CNS is critical for cortical and cognitive development. These processes may be particularly vulnerable to insults from the effects of the NICU environment (Kinney & Volpe, 2018b). Subplate neurons differentiate early and migrate to cortex from the germinal matrix to serve as guides for ascending and descending projections to target neurons. The subplate neurons provide critical connection sites for axons ascending from thalamus and other sites, until the neurons that these axons will eventually connect with have migrated from the germinal matrix. The subplate reaches its peak from 27 to 30 weeks (Kinney & Volpe, 2018b). Once cortical neurons have reached their eventual loci, they become arranged in layers and develop dendrites and axons that undergo extensive branching. The pattern of dendritic connections between neurons is a critical growth process that constitutes the "wiring" of the brain (also called arborization). These interconnections are critical for processing of impulses, cell-to-cell communication, and communication throughout the nervous system. Lack of connections can result in hypersensitivity, poorly modulated behaviors, and all-or-nothing responses, which can often be observed in preterm infants in the NICU. Similar behavior patterns can also be seen in some children in later infancy and childhood.

Organization also involves formation of connections or synapses between neurons and development of intracellular structures and enzymes for neurotransmitter production. Synaptogenesis is critical for integration across all areas of the nervous system. Synapses continue to restructure throughout development, and this process is thought to be the basis for memory and learning. Synaptogenesis is mediated by excitatory neurotransmitters such as glutamate. Glutamate acts on *N*-methyl-D-aspartate (NMDA) receptors to enhance neuronal proliferation, migration, and synaptic plasticity (du Plessis & Volpe, 2018). Another component of organization is reduction in the number of neurons and their connections through the death of many neurons and regression of dendrites and synapses. Neuronal death assists in elimination of errors within the nervous system, such as neurons that are improperly located, that fail to achieve adequate connections, or that are underused (Blackburn, 2018; du Plessis, Limperopoulos, & Volpe, 2018b). Finally, organization involves development of different types of glia cells, including astroglia, microglia, and oligodendrocyte (Kinney & Volpe, 2018b). Astroglia provide support for neurons, with axonal guidance, brain structural development and growth, blood–brain barrier function, and integration of information within the brain (Blackburn, 2018). Astroglia undergo rapid proliferation between 24 and 32 weeks' gestation (Poduri & Volpe, 2018b). Oligodendrocytes are the cells that produce myelin within the CNS. These glia are particularly vulnerable to hypoxic and ischemic injury prior to 32 weeks' gestation (premyelinating period; Kinney & Volpe, 2018b). Damage to the premyelinating oligodendrocytes is a prominent feature in WM injury in preterm infants (see Chapter 15, Neurologic System).

Organizational processes and modification of neurons continue into adulthood, but are particularly vulnerable during infancy. This ability of a neuron to change structure and function in response to external experiences and to store that information for memory and learning is referred to as neural (brain) plasticity (Blackburn, 2018; Fiori & Guzzetta, 2015). The neonate's brain is still under construction with enhanced plasticity. Enhanced plasticity of the

developing brain allows it to be influenced more strongly by the environment than the adult brain. However, this increased plasticity also creates selective brain vulnerability (Guyer, Pérez-Edgar, & Crone, 2018; Limperopoulos, 2010). The more immature the infant at birth, the greater the impact of neural plasticity. Sensory input influences later neuronal structures, processes, and responses that can translate to differences in the input, and those differences in the input further influence future developmental outcomes. New information and experiences will be filtered through processes and structures that have already adapted to previous input and experiences (Oakes, 2017). Plasticity in the preterm infant actually creates change in the input itself.

Adverse neonatal experiences may alter brain development during this vulnerable time and thus later development. Neuronal differentiation and organization are controlled by the interaction of genes with the environment. Each neuron has many synaptic connections that allow the brain to integrate and organize information. There is initially an overproduction of neurons and nerve connections. Many of these neurons and connections are later eliminated. Whether a connection is retained or eliminated is influenced by the infant's early environment and experiences. For example, the brain is more likely to strengthen and retain connections that are used repeatedly and to eliminate underused connections. Improper sensory input (too much or too little) or input that is inappropriate in terms of timing can alter brain development and structures. Thus, the environment of immature infants in the NICU and in the early months following discharge is critical for brain development and later cognitive function with a risk of alterations in neuronal networks, wiring, function, and behavior with exposure to early inappropriate sensory input (Fleiss et al., 2018; Kinney & Volpe, 2018b).

The human brain is arguably the most complex system in biology and yet its macroscopic layout is nearly complete by the time of term birth. The neonatal cerebral cortex displays a complex, adult-like gyrification pattern and all large-scale connections in the underlying WM are already in place (Kinney & Volpe, 2018b; Poduri & Volpe, 2018b). With the increasing availability of high-quality neuroimaging techniques, it is now feasible to study detailed early human brain development in vivo. Mapping the brain's anatomic and functional trajectories is crucial for early identification of altered development, since psychiatric and neurologic disorders may have a neurodevelopmental origin (Gao, Lin, Grewen, & Gilmore, 2017). These disturbances in brain development may be genetically programmed, epigenetically mediated, or environmentally influenced, and early detection may provide a window of opportunity for preventive strategies. These advances have led to exciting new insights into both healthy and atypical macroscale brain network development and have paved the way to bridge the gap between the brain's neurobiologic architecture and its behavioral repertoire.

Although the neurologic system is one of the earliest systems to develop in the embryo, it is not fully matured until adulthood. There are four areas of the nervous system function: autonomic, sensory, motor, and state regulation. All these areas develop before birth, yet maturation of these functions is not attained until after birth. Autonomic function includes self-regulation of respirations, heart rate (HR), temperature, and nutritional intake. The infant must adapt and respond to many changes simultaneously to survive in this new environment (Blackburn, 2018; Fink, Bronas, & Calik, 2018). The sensory system (discussed later) begins before birth, but maturation of each system continues after birth. In utero, the sensory systems develop in precise order, and for optimal development, that order should be unaltered. Tactile (touch) develops first, then vestibular, followed by olfactory (smell), gustatory (taste), auditory (hearing), and visual (sight), with neuroprotection for each system highlighted by Altimier and Phillips (2016). Motor function also begins before birth and is the result of coordination between neurodevelopment and muscular development. State regulation patterns after birth are individual; however, attentional abilities are reflective of the infant's increasing ability to habituate to the environment (Volpe, 2018).

The development of the brain, both structure and function, is shaped by the influence and interaction of four major factors: genetic endowment, internal or endogenous stimulation and sleep, external experiences and stimulation of the sensory organs, and the environment. The brain architecture, cell differentiation, cell migration, primary or initial cell location, and response to initial stimulation are directed by the genes or genetic endowment. Outside stimulation of the environment can influence or alter the expression or effect of a given gene. Epigenetics is changing the interpretation of "genetics" in relation to "environment," in that the genetic code is not exclusively responsible for the "destiny" of a child's development; environment also has a role in child development. Gene and environment interact over a lifetime and influence maturation of neural circuits and shape changes in physical and mental development. This property, called brain plasticity, is more prominent in early postnatal periods ("critical periods"), which are specific time windows when neural circuits display a heightened sensitivity in acquiring instructive and adaptive signals from the external environment. These periods are not a simple maturation process but represent a complex developmental system that involves different functions (visual, auditory, somatosensory, cognitive ones) and region-specific time courses within specific functional circuits (Inguaggiato, Sgandurra, & Cioni, 2017).

Spontaneous brain activity that occurs in the absence of outside stimulation during fetal neurodevelopment (internal or endogenous stimulation and sleep) occurs primarily during the last 20 weeks of gestational life. External experiences and stimulation of the sensory organs occur with each sensory system. The initial stimulation is internal or endogenous, but at a critical or sensitive point in development, outside stimulation and experience are needed for further development. Four components of the environment influence fetal, infant, and child development. These are the physical, chemical, sensory, and social/emotional environments. Events and stimuli from each of the four environments are capable of altering the course and outcome of developmental processes, which can be positive or negative (Graven & Browne, 2008).

Preterm infants in the NICU experience a very different pattern and type of sensory input than they would encounter in utero, and different from what the brain is expecting at any given GA. This creates a mismatch between the sensory environment of the infant and the requirements of the CNS for growth and development. Two types of neural plasticity have been proposed: experience-expectant and experience-dependent (Romeo et al., 2018; Rose & Bonhoeffer, 2018). Experience-expectant plasticity is linked to the brain's developmental timetable. Thus, specific sensory experiences and input are needed at specific times for neural development and maturation. Altered sequences or types of sensory input can modify or disrupt development. Experience-dependent plasticity involves interaction with the environment to develop specific skills for later use. This form of plasticity involves memory and learning and allows development of flexibility, adaptation, and individual differences in social and intellectual development.

The cerebellum is also vulnerable to insults from the early environment. The cerebellum is important in cognition and interconnections between different areas of the brain, including the thalamus, parietal lobe, and prefrontal cortex. The cerebellum undergoes a critical growth spurt from 24 to 40 weeks' gestation. This

spurt includes an increase in dendritic arborization, which is complete earlier than many other areas of the brain (see Chapter 15, Neurologic System). Insults may lead to altered cognitive function, language development, and behavioral development seen in some preterm infants (Bouyssi-Kobar et al., 2018; Brossard-Racine, du Plessis, & Limperopoulos, 2015; du Plessis Limperopoulos, & Volpe, 2018).

FETAL AND NEONATAL SENSORY DEVELOPMENT

The sensory system develops in a specific sequence: somatosensory (tactile and proprioceptive), vestibular, chemoreceptive, auditory, and visual. During fetal life, there is a lack of competing stimuli during rapid maturation of each system. For example, the infant develops chemoreception before the structures for hearing and vision are in place and after somatosensory and vestibular function has matured. Similarly, the hearing maturation in the fetus is most rapid during a time when vision is still immature and in an environment where vision is not being stimulated by light. Animal studies have demonstrated that out-of-sequence stimulation of one system interferes with development of not only that system but also other systems that are still immature. For example, in animal models inappropriate visual stimulation while hearing and vision are still developing may alter not only vision but also hearing development (Graven, 2011; Lickliter, 2011).

Tactile/Proprioceptive

Somatosensory and vestibular sensations mature early. The first sense to emerge during ontogenesis, around 8 weeks of gestation, is touch (Hooker, 1952). The developing fetus is constantly touched by its environment, the placenta, the umbilical cord, amniotic fluid, and the uterine surface, and touches its own body passively or actively as self-initiated movements develop. From 26 weeks of gestation, the fetus starts actively responding to vibration stimuli with HR acceleration (Kisilevsky, Muir, & Low, 1992) and increased movement rates (Kisilevsky, Gilmour, Stutzman, Hains, & Brown, 2012). Their reactivity to vibration steadily increases and then stabilizes by 32 weeks of gestation (Werchan, Baumgartner, Lewkowicz, & Amso, 2018).

The fetus prefers to touch body areas that are densely innervated and are more sensitive, such as the skin of the face with rich trigeminal innervation. Hand-to-face interaction appears early on around the mouth by 2 months of GA; hands become touch sensitive by 10 to 11 weeks. Nociceptors are found by 11 weeks, appearing first in the face, palms, and soles, are seen in areas such as the trunk, arms, and legs by 15 weeks, and are abundant by 20 to 22 weeks (Borsani, Della Vedova, Rezzani, Rodella, & Cristini, 2018).

Vestibular

Vestibular stimulation is mediated by receptors in the ear that detect changes in directions and rate of head movement and rotation. Vestibular system maturation reaches structural maturation by 14 to 20 weeks' gestation, with responses to vestibular stimulation seen as early as 25 weeks' gestation (Blackburn, 2018; Borsani et al., 2018). Fetuses display an arousal response to maternal "tactile stimulation," that is, when the mother touches her abdomen, and in particular during the third trimester, fetuses increase some of their movements as a response to the touch of the mother on her abdomen (Marx & Nagy, 2015). This differential response of the older fetuses might be due to the maturation of the CNS. During the third trimester of pregnancy, the CNS continues the maturation, neuronal differentiation, lamination, and the distribution of the thalamocortical axons. It is between the 26th and 28th weeks of gestation that the peripheral nervous system connections with the CNS become functional, which, in turn, allows the fetus to process and to react to external somatosensory and pressure stimuli.

Smell/Olfactory and Taste/Gustatory

Smell and taste are powerful sensory inputs that develop during fetal life and are important in the transition to postnatal feeding (Bloomfield, Alexander, Muelbert, & Beker, 2017). Olfactory receptor neurons are found in preterm infants as early as 24 to 27 weeks of gestation, and preterm neonates regularly respond to olfactory stimuli after 28 weeks' gestation (Sarnat, Flores-Sarnat, & Wei, 2017). Neonatal olfactory reflexes are most constant in wakefulness and light (active) sleep, but responses in deep (quiet) sleep may be diminished or absent. **Emergency Alert: Sedation induced by many medications, particularly antiepileptic drugs, also may suppress olfactory reflexes** (Sarnat et al., 2017). It is estimated that the mature human brain can discriminate a trillion odors (Bushdid, Magnasco, Vosshall, & Keller, 2014).

Olfaction is not only involved in guiding the human newborn to the nipple, but it also establishes infant attachment and parental bonding, and regulates child and adult social interactions (Bennett et al., 2017). In addition to the importance of smell in recognition of the mother, smell and taste initiate metabolic pathways that promote digestion and metabolic control (Bloomfield et al., 2017). Olfaction stimulates the digestive tract, improving tolerance of enteral feeds. Longer exposure of tube-fed preterm babies to smell or to smell and taste has been shown to shorten time to full enteral feeds as well as decreased hospital stay (Beker, Opie, Noble, Jiang, & Bloomfield, 2017; Bloomfield et al., 2017). A recent study by Cao Van et al. (2018) suggested that olfactory stimulation promoted a faster switch from feeding tube to satisfactory oral feeding in premature newborns, leading to a shortened length of hospital stay. The odor of maternal milk also appears to have an analgesic role in newborns (Zhang, Su, Li, & Chen, 2018).

Additionally, olfaction has been shown to impact the central appetite-regulatory pathways. Information on odor is passed from the olfactory bulbs to the primary olfactory cortex via the lateral olfactory tract. Functional MRI studies in adults demonstrate activation of the lateral and anterior orbitofrontal gyri (Adam-Darque et al., 2018). From there, information passes to the orbitofrontal cortex, where conscious perception of smell occurs, and also to the hypothalamus via the amygdala of the limbic system. Near-infrared spectroscopy (NIRS) studies in term and preterm neonates have demonstrated changes in cerebral oxygenation in the prefrontal area in response to odor stimulation This is assumed to reflect changes in blood flow and, therefore, neuronal activity (Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2009).

The smell experience can involve the costimulation of the olfactory and trigeminal subsystems, both of which are functional before the end of the second trimester of gestation. The branches of the trigeminal nerve are sensitive to chemo stimulants of higher concentrations, which are involved in the perception of different trigeminal components of odors like the coolness, the pungency, and the irritating sensation triggered by alcoholic vapors. Ambient odors in the hospital environment can modify the physiologic and behavioral stability of preterm infants. Exposure to NICU odors (NO) can trigger cerebral hemodynamic changes in the olfactory cortex. Most of these NOs are perceived as irritants and trigger the

trigeminal system (Lagercrantz & Changeux, 2010). Very preterm infants react to and cortically process NOs, with strong trigeminal properties, which triggers the trigeminal pain system inducing pain behaviors (Frie, Bartocci, Lagercrantz, & Kuhn, 2018).

Numerous artificial odors, originating from skin care or cleaning products, from handwashing or from the decontaminated hands of caregivers or parents, are introduced into incubators. Because of their chemical composition and their olfactory and/or trigeminal properties, some of them are more irritating than others. The most commonly reported smell is released from the hands after disinfection with aqueous alcohol solutions. These products emit an alcoholic vapor, especially when the hands are insufficiently dried, and the dissemination of volatile fragrances strongly stimulates the trigeminal subsystem.

In the NICU, preterm infants are not only exposed to strong odors from healthcare products but also to air-jet–induced trigeminal stimuli from respiratory devices, such as those that provide nasal continuous airway pressure. Repeated exposure to these trigeminal odors plays a role in the habituation process. Kuhn, Zores, Astruc, Dufour, and Casper (2011) found that infants' olfactory and/or trigeminal systems were stimulated an average of 44 times a day if the baby was breathing room air, or 60 times a day if he/she was mechanically ventilated. At their peak, newborns breathing room air and those mechanically ventilated were exposed 146 and 206 times a day, respectively. Very preterm infants were exposed to olfactory stimuli an average of 1,320 and 1,800 times during their first month of life (Kuhn et al., 2011).

Habituation to olfactory stimuli is considered a simple form of nonassociative learning, during which the response to nonrelevant stimuli declines (Freedman, Radhakrishna, Escanilla, & Linster, 2013). Research indicates that trigeminal and olfactory stimuli can induce habituation (Flohr et al., 2015).

The emotional content of odors is highly plastic, as it is modifiable by a few hours of mere exposure or by the pairings with reinforcers provided by caregivers (W. Liu et al., 2007). It has been shown that people can recall a scent with 65% accuracy after 1 year, because smells are processed by the same part of the brain that handles memories and emotions.

Enhancing the olfactory environment can be achieved through the utilization of olfactory neuroprotective interventions (NPIs). These positive NPIs may include maternal breast scent via a breast pad or a soft-scented cloth. Skin-to-skin contact (SSC) helps support the discrimination of maternal breast scent. Mouth care provided with mother's milk helps the infant recognize the mother's smell and associate that smell with food and feeding when the infant is able to nipple feed. **Quality and Safety: Minimizing an infant's exposure to irritating odors in the NICU environment through a more cautious use of odorous healthcare products, perfumes, colognes, or aftershaves is considered essential for the care of infants.** Alcohol wipes should not be opened near an infant's head, and preferably, should be opened outside of the incubator environment. The odor of tobacco on caregiver/family bodies and clothing should be avoided. NICU staff and parents should be educated on this topic to prevent olfactory overstimulation (Altimier & Phillips, 2016; Kuhn et al., 2011).

The taste buds appear by 7 to 8 weeks and receptors by 16 weeks. By term, the infant has adult numbers of receptors. Nasal chemoreceptors develop from 7 to 20 weeks' gestation and respond to the fragrant molecules in amniotic fluid. The composition of amniotic fluid varies with maternal diet and bathes both oral and nasal chemoreceptors. Exposure to substances from maternal diet may play a role in programming later dietary preferences. Fetal swallowing rates change with exposure to different taste in amniotic fluid. Preterm infants respond to different tastes and smells by at least 28 weeks' gestation and possibly earlier. Nutrient odor may also influence nonnutritive sucking. Term infants are able to detect, localize, and discriminate a variety of distinct odors and tastes. They respond preferentially to breast odors, their mothers' scents, and other odors associated with positive reinforcements (Beker et al., 2017; Bloomfield et al., 2017; Lipchock, Reed, & Mennella, 2011).

Olfaction and gustation are not only critical for the enjoyment of food, but also have important metabolic roles, initiating the cephalic phase response that sets in train secretion of hormones important for metabolism and digestion before any food is actually ingested (Bloomfield et al., 2017). Early colostrum administration in preterm babies has been determined to be safe, and some have reported increased rates of infants receiving breast milk as the majority of enteral feeds 6 weeks later (J. Lee et al., 2015; Snyder et al., 2017).

Consistent evidence supports the hypothesis of prenatal programming of postnatal specific appetites. Different mechanisms seem to program the developing brain in terms of acceptance or rejection of a given chemosensory stimulus that will later define feeding or searching patterns of a palatable substance (Faas, 2013). For example, extracellular dehydration during pregnancy is sufficient to induce a remarkable increase in the neonate's salt appetite that can persist until adulthood. Neonates are able to detect the smell of the amniotic fluid and of a milk formula with which they were fed. Yet, when both odorants are presented in a two-way preference test, the prenatal substrate elicits more behavioral orienting responses than the postnatal olfactory-related feeding substrate, demonstrating a significant neonatal preference for the prenatal odor (Faas, 2013). Children born preterm have been shown to respond positively to olfactory stimulation associated with their mother's breast milk (Yildiz, Arikan, Gozum, Tastekin, & Budancamanak, 2011).

Providing a pacifier with mother's milk has been shown to increase nonnutritive sucking, intake, and growth and to shorten the length of hospitalization (Foster, Psaila, & Patterson, 2016; Z. Greene, O'Donnell, & Walshe, 2016). When preterm infants were provided both the smell and taste of milk simultaneously, they had a significant improvement in milk tolerance and weight gain (Beker et al., 2017). Infants also demonstrate more suck attempts when looking at human faces in conjunction with maternal scent, indicating a potential link between social visual preference and suck behavior (Zimmerman & DeSousa, 2018).

Auditory

Auditory perception begins during fetal life and continues to develop until adolescence (Lahav & Skoe, 2014). The structures of the auditory system, including the inner ear and cochlea, are mature enough to support hearing by approximately 20 weeks' gestation. During fetal life, the ossicles (three small bones) of the middle ear cannot perform their amplifying, translational functions because outer, middle, and inner ears are all fluid filled. At this time, the hair cells of the inner ear are stimulated directly by vibrations of the fetal skull. Bone-conducted stimulation of the cochlear hair cells produces actual hearing and is not a "separate sense." The consequence of transmission of sound waves in this manner is similar to an adult hearing loss of about 40 dBA (Zubiaurre-Elorza et al., 2018).

With maturation and experience, as each hair cell in the cochlea becomes associated with a specific counterpart in the auditory brain centers, the individual frequencies are organized precisely in both inner ear and brain, just as the keys on a piano (Appler & Goodrich, 2011).

Fetal hearing is thought to begin at 24 to 25 weeks. In preterm infants, auditory evoked potentials can be recorded and responses to sound observed as early as 25 to 26 weeks (Z. D. Jiang & Chen, 2014). Auditory cortex development begins by the second trimester but is not mature until later in childhood. Maturation of the cochlea and auditory nerve increases from 28 weeks on. Initially, the hearing threshold is around 65 decibels with a range of 500 to 1,000 Hz, increasing with increasing GA to a threshold of 20 to 25 decibels and range of 500 to 2,000 Hz by term (Zubiaurre-Elorza et al., 2018). Between 28 and 34 weeks, the preterm infant develops the ability to begin to orient to sound, turning the head in the direction of an auditory stimulus, and showing evidence of arousal and attention (Lahav & Skoe, 2014; McMahon, Wintermark, & Lahav, 2012; Philben, 2017). During the third trimester, the cochlea continues to mature and develop its ability to hear sounds across frequencies. The hearing threshold decreases with GA. Infants prefer their own mothers' voices even before birth (Kisilevsky, 2016).

Visual

The eyes begin to develop early in the embryonic period (24–26 weeks) but continue anatomic and functional maturation into the third trimester and early infancy (Graven, 2011). Vision is the least mature sense at birth, and even full-term infants undergo significant continued maturation during infancy. The lens is initially cloudy; the second layer of the lens forms by 30 weeks, followed by the third and fourth layers. Immature infants are very myopic, and cone differentiation does not begin until after 30 to 32 weeks. Infants born extremely preterm (<27 weeks' GA) have reduced function of both rods and cones when compared with children born at term (Graven, 2011; Molnar, Andréasson, Larsson, Åkerblom, & Holmström, 2017). In extremely premature infants, there seems to be an arrest in the normal retinal development that appears to persist later into childhood and adolescence, with reduced rod and cone functions. Rod and cone disorders are known to result in night vision problems, loss of the visual field, reduced color vision, and photophobia (Molnar et al., 2017). Prematurely born infants and children born small for gestational age (SGA) are also at an increased risk of face recognition impairment and face delayed memory, both in early and late childhood, independently of their GA at birth (Perez-Roche et al., 2017).

By 22 weeks' gestation, the layers of the retina have formed rod differentiation, and retinal vascularization begins by 25 weeks' GA; myelination of the optic nerve begins at 24 weeks. By 26 weeks, visual cortex neurons are in place with rapid development of visual neuronal connections and processes between 28 and 34 weeks' gestation (Graven & Browne, 2008). Prior to 28 weeks, infants have little pupillary response. This response becomes more mature but is still sluggish between 30 and 34 weeks, and is mature by 36 weeks. The visual cortex undergoes rapid dendritic and synaptic development between 24 and 34 weeks. By 34 to 36 weeks, the visual cortex is similar to that of the term infant, but still immature, with significant development in the first year after birth (Graven, 2011; Neil & Inder, 2018).

Multisensory Processing

The newborn human arrives into a startlingly complex sensory world in which it is inundated with information from all of the sensory systems simultaneously: touch, proprioception, vestibular input, smell, taste, audition, and vision, all of which provide information about partially overlapping features of objects and events, in almost uniformly varying neural codes. If, as infants or adults, we are to perceive a spatiotemporally coherent and meaningful environment from this multisensory mixture, and furthermore make efficient use of sensory information, our developing sensory systems need to determine how, when, and when not to combine stimuli across modalities.

Until recently, the classic view of multisensory processing has been that cortical regions are inherently specialized, for example, sound information is only processed in the temporal cortex, and multisensory processing only occurs when modality-specific information reaches higher-order association areas. This view has been challenged by the alternative that (1) the neocortex is largely a multisensory organ, (2) occipital and temporal cortices have been found to respond to both auditory and visual stimulation, and (3) multisensory interactions occur not only in higher-order association areas, but also concurrently in the midbrain and in sensory-specific cortices (Werchan et al., 2018). Functional NIRS (fNIRS) was utilized to show that temporal and occipital cortices were functionally coupled and that the extent of this coupling during a synchronous, but not an asynchronous, audiovisual event predicted whether occipital cortex would subsequently respond to sound-only information. These data suggest that multisensory experience may shape cortical dynamics to adapt to synchronous multisensory information in the environment. These findings provide new insights into the developmental precursors of the cortical dynamics that occur whenever infants experience multisensory information in their environment. Furthermore, the findings show that exposure to concurrent (i.e., temporally synchronized) multisensory events in early infancy rapidly recruits responsiveness to the visual and auditory attributes that characterize everyday multisensory events. Since normal multisensory experiences consist of integrated audiovisual attributes, it is likely that long-term, everyday, integrated, multisensory experience tunes the occipital cortex to also respond to unrelated salient sounds by the time we become adults (Werchan et al., 2018).

Quality and Safety: Defining types, timing, and frequency of sensory-based NPIs that prevent harm and optimize infant outcomes can guide environmental modifications and individualize care needed for these vulnerable infants and their families.

A NPI that protects all of the senses is that of SSC, which provides the infant with tactile, vestibular/kinesthetic, olfactory, auditory, and at times visual sensory inputs. SSC in the NICU setting has been associated with increased physiologic regulation, improved oxygen saturation levels, and decreased length of NICU hospital stay. Dr. Nils Bergman (2015) and others have made a strong case for the neurosupportive nature of SSC between newborn infants and their parents. "The optimal environment for any newborn, but particularly for the premature infant, is skin-to-skin contact with mother (or father), also known as kangaroo care" (Bergman, 2015). For all primates, the mother's womb is the normal environment where development begins and the mother's body is the normal environment where development continues after birth. In SSC, the newborn receives salient and expected sensory inputs that lead to physiologic regulation and a secure attachment, processes that are both mediated by the limbic system and essential for normal development. Dr. Bergman (2015) asserts that SSC is, therefore, not a care practice but is a place where all neuroprotective care practices would ideally be done. SSC is not an intervention but is our biologic default.

Because of the well-documented high level of stress to the newborn caused by separation from the mother, Dr. Bergman (2014) recommends zero separation. There are situations whereby a mother and infant must be separated, particularly if the mother is ill or unable to be present; however, zero separation is the biologic default and should be the goal. Bergman et al. have provided convincing evidence in two randomized controlled trials that healthy

preterm infants are more physiologically stable in SSC with their mothers during the first 6 hours after birth than separated from their mothers while inside an incubator (Luong, Nguyen, Thi, Carrara, & Bergman, 2016).

NEONATAL NEUROBEHAVIORAL DEVELOPMENT

In the past decades, our knowledge of early childhood development has been dramatically altered by an avalanche of new research in neurobiology, behavioral, and social sciences that has led to major advances in understanding the conditions that influence the well-being and early development of infants and young children. A deeper understanding of the importance of early life experience and the highly interactive influences of genetics and the environment on the developing brain has deepened our understanding of the early years. Attention to the powerful influence of the role of early relationships and the capabilities of the development of emotions in young children has finally taken center stage. Add to this the changes in our social structures and changes in our families, culturally and economically, including the shifting of parenting roles, along with changes in the workplace and in child care services for the very youngest, and the continuing high levels of economic hardship in many families, and it becomes clear that a professional review and rethinking of policy and practice requires dedicated attention and a thoughtful response.

Parents become the "coregulators" or extensions of the infant's internal regulatory systems working to regulate function in the infant just as he or she is working toward the same (Hofer, 2010). This requires of caregivers the ability to read and understand the infant's needs and the sensitivity, knowledge, and energy to respond in helpful, satisfying ways. Parents must establish "regulatory connections" with young children and then shift the independent task of regulation gradually over to them, one domain and one day at a time, being forever watchful that the balance in the child is not seriously disrupted. The ways that infants and young children learn about self-management involves behavioral, emotional, and cognitive self-control, which must evolve for competent functioning.

During early child development (birth to 6 years), children become consistently independent and develop the ability to manage their own behavior. Two concerns related to these developmental processes are sleep behavior and crying behavior. Infants with serious medical conditions that require intensive care, including preterm or medically fragile infants, have more difficult transitions to regulatory competence. Immature sick newborns are much less able to organize and stabilize sleep, waking, and feeding. They tend to be unpredictable, to cry more, and to be fussier. They tend to make less eye contact, smile less, vocalize less, and show less positive affect, and they are generally more difficult and harder for parents to read. During the first 3 months after birth for a full-term newborn, the infant depends on the relationship with the primary caregiver. The infant takes on an extensive undertaking that requires that he or she learn to get to sleep without help, stop crying when consoled, respond to the caregiver, and establish day–night, wake–sleep rhythms. Once the rapid developmental changes of the first 3 months of life after full-term birth are accomplished, the infant faces another level of regulation in controlling his or her emotions and behavior. Followed by the regulation of attention and the regulation of mental processes, a process known as executive function emerges and involves the ability to think, retrieve, and remember information, solve problems, and engage in complex activities, which involve oral language, reading and writing, math, and social behavior.

Early experiences clearly affect the development of the brain. Development begins during early fetal life and lays a foundation for all that is to follow. Als (1982, 1986) and colleagues developed a model, the Synactive Theory of Development, for understanding the organization of neurobehavioral capabilities in the development of the fetus and newborn infant. This model describes emerging behavioral organizational abilities of the neonate. This model is based on the assumption that infants actively communicate via their behavior, which becomes an important route for understanding thresholds of stress or stability. Behavior of the infant not only is the main route of communication but also provides the basis for the structure of developmental assessment and provision of developmentally appropriate care (Als, 1986).

This synactive theory of development provides a model through which one can specify the degree of differentiation of behavior and the ability of infants to organize and control their behavior. The focus is not on assessment of skills, but on the unique way each individual infant deals with the world around her or him. The synactive theory of development specifies the range of neonatal behavior as the infant matures as well as the ability of the infant to regulate behavior. This model is based on the assumption that the infant's primary route of communicating both functional stability and the limits for stress is through behavior. For example, infants who extend their limbs after being turned to supine to have their diaper changed may be communicating that they cannot control their limbs and movement in that position. Containing the limbs of these infants helps them to develop control and reduces stress over the loss of control (Als, 1986; Lawhon & Als, 2010).

Infants are seen as being in continual interaction with their environment via five subsystems: autonomic/physiologic, motor, state/organizational, attentional/interactive, and self-regulatory. These subsystems mature simultaneously, and within each subsystem a developmental sequence can be observed. Thus, at each stage of development, new tasks and organizations are learned against the backdrop of previous development. The subsystems are interdependent and interrelated. For example, physiologic stability provides the foundation for motor and state control; the infant cannot respond socially to caregivers until motor and state control is achieved. The loss of integrity in one subsystem can influence the organization of other subsystems in response to environmental demands. In the preterm, less organized infant, the systems interplay, continuously influencing each other. In the healthy full-term infant, these systems are synchronized and function smoothly. Thus, full-term infants can regulate their autonomic, motor, state, and attentional systems with ease and without apparent stress. However, less mature infants tend to be able to tolerate only one or minimal activity at a time and may easily lose control if their individual thresholds are exceeded. Instability in the autonomic system can be seen in the pattern of respiration (pauses, tachypnea), color changes (red, pale, dusky, mottled), and various visceral signs (regurgitation, twitching, stooling). Organization of the motor system is assessed by observing the infant's tone and posture (flexed, extended, hyperflexed, flaccid); specific movement patterns of the extremities, head, trunk, and face; and level of activity. The development of motor responses is closely linked to state organization (Als et al., 1994).

The state system is understood by noting the available range of states of consciousness (sleep to arousal, awake to alert, crying), how well each state is defined (in terms of behavioral and physiologic parameters), transitions between states, and the quality of organization of these states.

States may be poorly defined at first, especially in the immature infant (Whitehead, Laudiano-Dray, Meek, & Fabrizi, 2018). For example, jerky body twitches and fussing may accompany sleep and wake states. In addition, the immature infant may not be able to achieve clearly defined states as seen in the mature infant (see section on Sleep–Wake States). Initially, preterm infants tend to be unstable and fragile, with sudden changes in their autonomic, motor, and state systems. These infants often have minimal response to handling or other sensory input until a threshold is reached, then quickly develop a cascade of responses, ending in several color changes, flaccidity, bradycardia, and apnea. As the infant matures, the responses are more variable, and the infant is less likely to totally decompensate (Als, 1986). **Quality and Safety: Changes within the autonomic, motor, and state systems at all stages of development are not just reactions to stress and overstimulation, but can signal that the infant's tolerance threshold has been exceeded. By recognizing these signs early, the nurse can intervene to prevent mild to severe decompensation.**

The attentional/interactive system involves the infant's ability to orient and focus on sensory stimuli, such as faces, sounds, or objects—that is, the external environment. This system also includes the range of abilities in states of consciousness: how well periods of alertness are defined and how transitions into and out of alertness are handled. At first, this alertness may be very brief, with a dull look or glassy-eyed stare. As this system matures, the infant is able to interact with greater ease and for longer periods. Social responsiveness requires that the infant have enough state control to sustain some awake and alert states (Als, 1986). The self-regulatory system includes behaviors the infant uses to maintain the integrity and balance of the other subsystems, to integrate the other systems, and to move smoothly between states. For example, some infants can tuck their limbs close to their body in an effort to gain control when stressed, whereas others seem to relax if they can brace a foot against the side of the crib.

In summary, the process of development appears to be that of stabilization and integration of some subsystems, which allows the differentiation and emergence of others that in turn provide feedback for the integrated system. In this process, the whole system is reopened and transformed to a new level of more differentiated integration, from which the next newly emerging subsystem can further differentiate and press to actualization and realization (Als, 1986). By observing and assessing the newborn infant's responses to the caregiver and other aspects of the environment across these five subsystems of behavioral functioning, one can develop and implement a plan of care to support the infant's emerging neurodevelopmental organization and reduce stress. The NICU staff, especially nurses, play a significant role in shaping the environment and making caregiving more responsive to infants. This requires careful observation and documentation of infant behavior as is given to physiologic status and development of an individualized plan of care. Infant responses to the environment will be influenced by factors such as state; basic needs (e.g., hunger); sensory threshold; parameters of the animate and inanimate environment, including readability, predictability, and responsivity; infant health status; and level of neurobehavioral maturity.

Infant behavioral responses include specific autonomic, motoric, and state cues, which indicate disorganization and stress and the need for immediate intervention, and stability and self-regulatory cues, which indicate that the infant is coping positively. Thus, cues provide information about an infant's needs and status, handling of sensory input, stress and sensory overload, tolerance for stimuli, and need for rest and time-out. Table 31.1 provides examples of infant cues.

TABLE 31.1

EXAMPLES OF INFANT NEUROBEHAVIORAL CUES

Stability Cues/Engagement Cues	Stress Cues/Disengagement Cues
Alertness, attention, orienting to people and objects	Altered vital signs (heart rate, respiratory rate)
Arm and leg flexion	Arching
Eyes open, alert	Color changes or visceral signs such as spitting
Grasping	Diffuse states, rapid state changes
Hand to mouth activity	Finger splay
Modulated states and state transitions	Flaccid or hypertonic tone
Modulated tone and movement	Frantic activity
Self-consoling activities	Grimacing
Stable vital signs, color	Hand to face or ear
Stable visceral and motor signs	Staring, averting gaze Tremors or jitteriness

Assessment of Neonatal Neurobehavioral Development

Developmental assessment of newborn functioning emerged with the awareness of the amazing capabilities of neonates. The newborn infant, who for years was thought to be nonreactive and incapable of social participation, is now seen as an active participant in social interaction and capable of self-regulation. Even with a greater understanding of newborn capabilities, researchers and clinicians have been unable to consistently predict the future course of an infant's development from early neurologic or behavioral assessments. Thus, there is no one comprehensive assessment tool for all infants (El-Dib, Massaro, Glass, & Aly, 2011). Historically, two types of neonatal assessments have evolved—the neurologic examination and the behavioral examination. The neurologic examination assesses the function of the CNS and typically includes assessment of motor tone and reflex behaviors within the context of infant state. The behavioral examination complements and elaborates on the neurologic assessment. An assumption underlying the behavioral examination is that the observable behavior of an infant is a reflection of his or her underlying neurologic status. The behavioral examination seeks to describe the quality of behavioral performance. More recently, these two forms of assessment have been combined into the neurodevelopmental or neurobehavioral assessment.

The neurodevelopmental examination is important because it yields a large pool of early observable behavior, including information about the infant's neurologic status and abilities to cope and

interact with the environment. In addition, data from this examination can assist the clinician in estimating maturity and in identifying and evaluating problems that could be precursors to later developmental problems. Because the neurodevelopmental examination provides an immediate basis for determining the status of the infant's development, the results can be used for planning intervention strategies as well as for screening for infants in need of further diagnostic assessments and early intervention.

Who Needs to Be Assessed?

All neonates and their caregivers can benefit from ongoing neurobehavioral assessment. These assessments provide information on the infant's behavioral capabilities, interactive qualities, and adaptations to the extrauterine environment. This information can be used in planning care, developing individualized intervention strategies, modifying care as the infant matures, and parent teaching and other activities to promote parent–infant interaction. However, for some infants, neurodevelopmental assessment is critical for documentation of neurodevelopmental status, screening, and early case finding.

Certain groups of infants are at increased risk for developmental disabilities and later cognitive impairment (Adams-Chapman et al., 2018; Younge et al., 2017). Infants that fall into the highest risk category include very low birth weight (VLBW) infants and those with significant intracranial hemorrhages. Preterm infants with known sensory impairment and chronic illness are also at risk for later cognitive dysfunction. Infants with respiratory distress syndrome (RDS) are at greater risk if they also develop CLD. Severe BPD is generally associated with a prolonged and complicated hospital course, increasing the risk for later neurodevelopmental problems. Surgical NEC is also associated with adverse neurodevelopmental outcome (Adams-Chapman et al., 2018). Preterm infants as a group are at greater risk than term infants of comparable postmenstrual ages. Preterm infants often exhibit manifestations of altered brain organization, including disrupted sleep, difficult temperament, both hyperresponsivity and hyporesponsivity to sensory input, prolonged attention to redundant information, inattention to novel stimuli, and poor quality of motor function (Chorna, Solomon, Slaughter, Stark, & Maitre, 2014). These precursors of learning problems in school are not fully explained by either the severity of illness among preterm infants or later conditions in the home environments.

Neurobehavioral Assessment in the NICU and Early Infancy

For high-risk newborns, early assessment of neurobehavior that accurately predicts neurodevelopmental outcome is the first step toward determining early intervention needs. Neurobehavioral assessment can be performed at several different levels and is an essential part of comprehensive care of the high-risk infant in the NICU. Individuals such as Brazelton, Als, and their colleagues have sought to assess preterm and full-term newborn behavior and adaptations. Their work is based on an understanding of newborns as competent individuals with emerging developmental processes, who are engaged in dynamic interactions and negotiations with their environment. As a result, several tools have been developed to describe and quantify neurobehavioral organization of both preterm and full-term newborns.

Tools for neurobehavioral and neuromotor assessment include Amiel-Tison neurological assessment at term (ATNAT), assessment of preterm infants' behavior (APIB), Brazelton neonatal behavioral assessment scale (NBAS), neonatal intensive care unit network neurobehavioral scale (NNNS), Prechtl's assessment of general movements (GMs), neurobehavioral assessment of the preterm infant (NAPI), Dubowitz neurologic assessment of the preterm and full-term infant (Dubowitz), neuromotor behavioral assessment (NMBA), and the test of infant motor performance (TIMP; Als, Butler, Kosta, & McAnulty, 2005; Als, Lester, Tronick, & Brazelton, 1982; Amiel-Tison, 1976; Brazelton & Nugent, 2011; Campbell, 2005; Carmichael, Burns, Gray, & O'Callaghan, 1997; Dubowitz, Ricciw, & Mercuri, 2005; Einspieler & Prechtl, 2005; El-Dib et al., 2011; Korner & Constantinou, 2001; Lester, Tronick & Brazelton, 2004; Noble & Boyd, 2012; Snider et al., 2005). Several assessments for neurobehavioral assessment are described further. A recent analysis found that all of these measures "demonstrated adequate content and construct validity" (Noble & Boyd, 2012). The authors concluded that in the absence of a criterion standard for neonatal neuromotor assessments, the NNNS and APIB have strong psychometric qualities with better utility for research. Similarly, the GMs, TIMP, and NAPI have strong psychometric qualities but better utility for clinical settings. The GMs and TIMP showed the strongest associations with neurodevelopmental outcome (Craciunoiu & Holsti, 2017). The tools that are described here are the NBAS (Brazelton & Nugent, 2011); the APIB (Als, 1982; Als et al., 2005); the NNNS (Lester & Tronick, 2004); and the NAPI (Korner & Constantinou, 2001; Snider et al., 2005).

Brazelton Neonatal Behavioral Assessment Scale. The NBAS is a comprehensive behavioral assessment of the healthy full-term neonate containing six clusters with 28 behavioral items and 18 reflex/motor items. The NBAS combines evaluation of basic reflex responses with the integration of motor capacity, state regulation, and interactive abilities (Brazelton & Nugent, 2011). Infants are followed through the various states of sleep, arousal, and wakefulness and assessed on their ability to self-regulate in the face of increasingly vigorous activity. A primary focus is observation of the infant's individual and unique ability to respond to outside stimulation while regulating responses to and coping with pleasurable or stressful situations. The infant's best performance is scored. The results are an assessment of the infant's ability to (1) organize states, (2) habituate to external stimulation, (3) regulate motoric activity in the face of increasing sensory input, (4) respond to reflex testing, (5) remain alert and oriented to visual and auditory stimuli, (6) interact with a caregiver, and (7) self-console.

The NBAS has been used in numerous studies of neonatal behavior, including investigations of cross-cultural differences, characteristics of drug-addicted infants, effects of obstetric medication, and aspects of maternal–infant interaction (Brazelton & Nugent, 2011). An especially valuable use of the NBAS for nurses and other clinicians is as an intervention. For example, when an NBAS is performed in front of the infant's parents, the parents become increasingly aware of and amazed at the remarkable abilities of their infant. An understanding of their newborn's capacity to interact visually, turn to their voices, regulate state and motor activity, and self-console expands the parents' perception of the infant as a unique, competent individual and enhances parent–infant interaction (Brazelton & Nugent, 2011).

The newborn behavioral observations system (NBO) is another tool from this group that provides a series of 18 neurobehavioral observations for clinicians and parents to observe the infant together and determine the infant's capabilities and needs. The NBO is a neurobehavioral observation tool designed to sensitize parents to infants' capacities and individuality and to enhance the parent–infant relationship by strengthening parents' confidence and practical skills in caring for their children. The NBO's focus on

relationship building is intended for infant mental health professionals who strive for a relational, family-centered model of care versus a pathology-based model (Nugent, 2007; Nugent, Bartlett, Von Ende, & Valim, 2017).

In response to a need to identify the preterm infant's neurobehavioral repertoire, the NBAS was expanded and modified for use with low birth weight infants. Items were added to the original scale, including difficulty of elicitation of alerting, degree of facilitation necessary to support the infant, control over stimulation, robustness, endurance, degree of exhaustion, quality of alertness, and balance of tone (Brazelton & Nugent, 2011; Nugent et al., 2017). These subscales are also useful in describing at-risk full-term infants, such as drug-exposed infants.

Assessment of Preterm Infant Behavior. The APIB was developed to respond to the need for a more discrete and comprehensive assessment of preterm infant functioning. The APIB is based on the Synactive Theory of Development, which describes the early behavioral organization and development of the neonate. The APIB is particularly useful for the preterm and full-term high-risk infant from birth to 44 weeks' postmenstrual age. The purpose of this assessment is to determine organization of the CNS and how infants cope with the intense environment of the NICU. The focus of the APIB is not only assessment of skill performance or specific responses to various stimuli, but also the unique way each individual infant deals and interacts with the world around him or her. As described previously, infants are seen as being in continual interaction with their environment and as communicating their responsiveness via five subsystems (autonomic, motor, state, attentional, and self-regulatory; Als, 1986; Als et al., 2005).

The APIB consists of six packages or sets of maneuvers adapted from the NBAS. The packages are organized to provide increasing input with which the infant must react, starting with stimulation while the infant is asleep to assess habituation. Subsequent packages move through maneuvers ranging from low and medium tactile manipulations to high tactile and vestibular handling. Throughout the assessment, the infant is continually observed for responses related to each of the five subsystems. Thus, the infant is observed and scored on each of the five subsystems and for examiner facilitation (ability to use support) before, during, and after administration of the items in each package. These responses are called the system scores and range on a nine-point scale from organized (1) to disorganized (9).

The APIB has been used for research and clinical purposes. As a research tool, it has been used to describe and identify neonatal behavioral organization in preterm and other high-risk infants (Als, 1986; Als et al., 1982, 2005). Clinically, psychologists, neonatologists, neurologists, nurses, developmental specialists, and therapists have used the APIB to provide consultation in the NICU regarding developmental interventions for specific infants. The APIB has recently been used to examine the neurobehavioral functioning in preterm infants diagnosed with IVH grades III and IV (Barbosa & Powlesland, 2018). The APIB is useful in determining an infant's degree of fragility and ability to tolerate different caregiving parameters. By measuring maturity of the five subsystems, one can determine maturity of each system and tolerance for handling as well as generate developmental care plans specific to each infant at that stage of development. The APIB is also useful in assessing infant readiness for changes in caregiving routines and in the physical and social environment. Assessing the degree of fragility and tolerance for activities can provide an invaluable piece of information about the infant's functional level and assist staff in making decisions about whether to protect the infant or to advance to the next level of care, as is illustrated in the following case.

A 28-week preterm infant had just been extubated and graduated to oxygen by nasal cannula and moved from the open bed to the incubator. An APIB revealed a responsive infant but one who was working extremely hard to regulate his system amid two major changes: extubation and change of physical environment. Although successful regulation was noted, it was also apparent that the infant was at maximal capacity in organizing himself. He showed efforts to suck and maintain hand to mouth; however, he could not maintain these postures for long without help. It was apparent that the infant's threshold had been reached and that any more change or stress would have caused a loss of control in his system's integrity. Immediately after the assessment, the neonatologists ordered nipple feedings once a day. With this new demand, the examiner felt that this infant would exceed his threshold and be unable to regulate himself. The developmental specialist recommended waiting 1 week for the infant to stabilize and to integrate his new experiences before taking on any new demands. This recommendation was not followed, and feeding continued. Two days later, the developmental specialist returned and noted that the infant had a trial of nippling. He had desaturated, become bradycardic, required bag-mask ventilation, and was considered to have "flunked" nippling. The order was terminated, with the plan to try again in a week. When feeding was reordered a week later, the infant tolerated it well.

Training in the APIB (www.nidcap.com) is extensive and requires knowledge of the NICU, including care practices and routines, staffing patterns, and typical infant experiences in that setting as well as physiologic limitations and medical problems. Interrater reliability, and concurrent and construct validity have been reported (Als et al., 2005).

Neonatal Individualized Development Care and Assessment Program. The NIDCAP incorporates several levels of developmental training in assessment techniques and intervention planning for high-risk preterm and full-term infants. Included in this program is an observation tool (level 1 NIDCAP naturalistic behavioral observation), which is extremely useful for the NICU nurse. This assessment involves an observation of the infant before, during, and after a routine caregiving episode. It provides the NICU nurse with information on the infant's individual cues for both stress and stable, organized function. The nurse can then structure the infant's experiences, including caregiving interventions and the physical and social environment, to support the infant at the current level of tolerance. This support includes an awareness of the timing of caregiving events, sequencing events, and interventions to prevent or reduce stress as well as to enhance stable behavior. Support for parents in understanding their infant's unique behavior and needs is also provided (Lawhon & Als, 2010; Lawhon & Hedlund, 2008).

NIDCAP training involves didactic sessions and clinical demonstration of the observational tool, after which the trainee completes a specified number of observations on infants of different GA, postbirth age, and health status. This observation period is followed by an assessment of reliability for certification by the trainer.

NNNS. The NNNS was developed for use with preterm and other at-risk infants such as those with perinatal drug exposure to measure the process of neurobehavioral organization, capturing both the normal range of behaviors and those present in high-risk infants (Lester et al., 2004; Lester & Tronick, 2004). The NNNS builds on several earlier assessments, including the neurologic examination of the full-term newborn infant (Prechtl, 1974; Prechtl & Beintema, 1968), abstinence syndrome scoring, and several of the assessments described in this section (NBAS, APIB, and NAPI;

Lester & Tronick, 2004). The NNNS can be used with infants from about 30 weeks' gestation to 46 to 48 weeks' postmenstrual age and assesses both behavioral function and neurologic integrity: (1) neurologic status (active and passive muscle tone, primitive reflexes, and CNS integrity); (2) behavioral state, sensory, and interactive responses; and (3) stress/abstinence scale. Items are administered only if the infant is in an appropriate state for that item. Administration of the assessment takes about 30 minutes (Lester & Tronick, 2004; Lester et al., 2004). More recently, a complex pattern of stability and change emerged when comparing NNNS summary scores from birth to 1 month. Orienting, regulation, and quality of movements significantly increased, whereas lethargy and hypotonicity significantly decreased, demonstrating that birth-to-1-month changes in NNNS performance suggest improvements in neurobehavioral organization (Provenzi et al., 2018). These data are useful for research purposes and for clinical evaluation of neurobehavioral performance in both healthy and at-risk 1-month-old infants.

NAPI. The NAPI is an assessment developed at Stanford University to assess the differential maturity of infants between 32 weeks' postconceptional age and term (Korner & Constantinou, 2001; Korner, Constantinou, Dimiceli, Brown, & Thom, 1991). Components include assessment of behavioral states, active tone, strength, reflexes, excitation and inhibition proneness, and orientation to visual and auditory stimuli. The NAPI has been used to monitor the developmental progress, to identify persistent lags in development, as an outcome measure in intervention studies and other studies, to describe individual differences in preterm infant development, and to identify infants with neurobehavioral alternations. The reliability and validity of this test and normative data have been established (Gorzilio, Garrido, Gaspardo, Martinez, & Linhares, 2015; Hyman, Snider, Majnemer, & Mazer, 2005; Korner et al., 1991; Korner & Constantinou, 2001; Snider et al., 2005).

Assessment Beyond Neonatal Development

As the infant matures, moves out of the neonatal period, and becomes a "long termer" in the NICU with chronic respiratory or other problems, neurodevelopmental assessments continue to provide important information. For the infant who requires prolonged hospitalization, a developmental assessment at the bedside can provide information on how the infant interacts with objects and people, organizes behavior, and copes with the environment, as well as on the infant's neurologic status. No formal developmental assessments have been standardized for these NICU populations. Most developmental psychologists or specialists adapt items from other examinations such as the Bayley Scales of Infant Development II (Bayley, 1993) or the more recent Bayley Scales of Infant and Toddler Development (Bayley, 2005). A recent study utilizing the *Bayley Scales of Infant and Toddler Development*, Third Edition (Bayley-III) suggested that corrected age for infants born preterm be applied differently in cognitive, language, and motor domains; correction for GA should be applied for the cognitive domain only, whereas for the motor domain, chronologic age should be used (Morsan, Fantoni, & Tallandini, 2018).

Because of the nature and severity of their illnesses, these infants may not be able to tolerate a complete examination at one session. To learn about the infant's behavioral capabilities and coping abilities adequately, the examiner must consider events that occurred for several hours before the assessment and be aware of the environment in which the infant normally lives and of his or her usual types of sensory experiences. Important areas of assessment include (1) availability of alerting, (2) ability to use interventions for consoling or developmental activities, (3) self-soothing capacity, (4) motor activities and strengths, (5) tolerance for handling (how long? with whom?), (6) degree of fragility, (7) degree of distractibility, (8) hand use, (9) parts of body available for use, and (10) respiratory capacity.

Sleep–Wake States

Another aspect of neurobehavioral development that is considered a part of any developmental program is sleep–wake states and how they affect responses to stimuli. Sleeping and waking states are clusters of behaviors that tend to occur together and represent the level of arousal of the individual, the individual's responsivity to external stimulation, and the underlying activation of the CNS. Three states have been identified in adults: wakefulness, non-(rapid eye movement) REM sleep, and REM sleep. In infants, it is also possible to identify states within waking and states that are transitional between waking and sleeping, because infants are less able to make rapid changes between states than adults. Infants also have more difficulty sustaining alertness when awake. Because the electrophysiologic patterns associated with sleeping and waking states in infants are somewhat different from those in adults (Heraghty, Hilliard, Henderson, & Fleming, 2008), the sleep states are usually designated active and quiet sleep, rather than REM and non-REM sleep (Raju & Radtke, 2012).

The development of organized sleep–wake states is a major feature of the neonatal period and developing infant. Although subsequent changes in the sleep–wake cycle with age are less profound, they represent predictable physiologic changes occurring as a function of age. Similarly, there are characteristic EEG patterns seen as a function of maturity in the neonate and developing child. These EEG changes continue to evolve into adulthood, offering an electrophysiologic marker of brain development.

Neonatal nurses need to be aware of the infant's present sleep–wake state and typical sleep–wake patterns when making assessments, because infant behavior and physiology are affected by state. The functioning of cardiovascular, respiratory, neurologic, endocrine, and gastrointestinal systems differs in different states. Moreover, sleeping and waking states affect the infant's ability to respond to stimulation. Thus, infant responses to nursing interventions and to parental interactions depend to a great deal on the infant's state when the stimulation begins. Also, during kangaroo care, infants exhibit more quiet sleep than when alone in the incubator (M. S. Scher et al., 2009). Timing routine interventions to occur when the infant is most responsive is an important aspect of some current systems of individualized nursing care (Becker, Grunwald, Moorman, & Stuhr, 1991; Bertelle, Mabin, Adrien, & Sizun, 2005). Finally, studies have indicated that sleeping and waking patterns are closely related to neurologic status (Heraghty et al., 2008). Thus, aberrant sleep–wake patterns could potentially be used to identify infants at risk for neurologic complications or poor developmental outcome.

State Scoring Systems. In adults, sleeping and waking are usually scored by EEG. However, because of the neurologic immaturity of infants, EEG is less reliable and needs to be combined with observation. When EEG and behavioral scoring of states in preterm infants are compared, there is a high degree of agreement (Sahni, Schulze, Stefanski, Myers, & Fifer, 1995; Sevestre, Oger, Bertelle, Mabin, & Sizun, 2013). Thus, by directly observing infants, whether full term or preterm, and identifying global categories that are made up of a number of specific behaviors that tend to occur together and reflect a similar level of arousal and responsiveness to the environment, nurses can validly score sleeping and waking states in newborn infants. The behaviors

that seem to be most important for scoring are respiration, eye movements, and motor activity (Brandon & Holditch-Davis, 2005; Tilmanne, Urbain, Kothare, Wouwer, & Kothare, 2009).

Nurse researchers currently use four standardized systems for scoring behavioral observations of sleep–wake states. The systems were developed by Brazelton (1984), Thoman (1990), Als et al. (1982), and Anderson (1999). These systems define states in very similar ways and are probably equally useful for clinical purposes. Table 31.2 presents a comparison of the state definitions used in these systems.

Clinicians and researchers differ in the ways they use these scoring systems. Neonatal nurses spend a lot of time observing infants and altering their care in response to infant behavioral changes. Experienced clinicians are undoubtedly already familiar with the characteristics of sleeping and waking states in these infants, even though they may be unable to name specific states. Thus, all they need to do to include judgments of sleeping and waking states is to use the state definitions of any standardized scoring system to systematize their clinical impressions.

For research, however, it is essential that the investigator receive training in the use of a particular scale so that it is used reliably. Clinicians reading research need to understand the differences among the scoring systems so that they can better interpret the findings and understand reports using different names for the same sleep–wake state. While many of these tools were described in previous sections, this discussion focuses on the scoring and emphasizes sleep-wake states.

Early State Scoring Systems. Sleeping and waking scoring systems for infants originated in the work of neurologists, pediatricians, and behaviorists in the 1960s. The neurologists needed a way to systematize the observations they made along with EEG studies, and behaviorists and pediatricians were particularly interested in the waking states and the effect of state on responsiveness to stimulation. Wolff (1959, 1966), a pediatrician, conducted extensive observations of newborn infants in the hospital and at home. As the result of his observations, he proposed a seven-state system. Prechtl and Beintema (1968), pediatric neurologists, proposed a simple five-state system that could be used either to score observations made along with EEG or to ensure that motor reflexes were elicited under optimal conditions. Finally, a team of pediatricians and neurologists at the University of California at

TABLE 31.2

APPROXIMATE EQUIVALENCE OF THE FOUR MAJOR SLEEP–WAKE STATE SCORING SYSTEMS

Brazelton	Thoman	Als	Anderson
6. Crying	Cry	6B. Lusty crying	12. Hard crying
		6A. Crying	11. Crying
5. Considerable motor activity	Fuss	5B. Considerable activity	10. Fussing
	Nonalert waking activity	5A. Active	9. Very restless awake
			8. Restless awake
4. Alert	Alert	4B. Bright alert	7. Alert inactivity
		4AH. Hyperalert	
		4AL. Awake and quiet	
3. Drowsy	Daze	3B. Drowsy	6. Quiet awake
	Drowse		5. Drowsy
	Sleep–wake transition	3A. Drowsy with more activity	4. Very restless sleep
2. Light sleep	Active sleep	2B. "Noisy" light sleep	3. Restless sleep
	Active–quiet transitional sleep	2A. Light sleep	2. Quiet sleep: irregular respiration
1. Deep sleep	Quiet sleep	1B. Deep sleep	1. Very quiet sleep
		1A. Very still deep sleep	

Note: Because the criteria used by these systems differ and because they are based on different conceptual frameworks, exact equivalence among them is not possible. Isolated instances of infant behavior may be scored quite differently than suggested by this table.

Los Angeles (UCLA) developed a manual to define the behavioral and EEG criteria for sleeping and waking (Anders, Emde, & Parmelee, 1971). These are still in use today, and each behavioral state scoring system currently in use is a refinement of these earlier systems.

Brazelton's State Scoring System. T. Berry Brazelton was a pediatrician from Harvard University in Cambridge, Massachusetts. He and his colleagues developed a state scoring system to be used as part of a behavioral evaluation of newborn infants, the NBAS (Brazelton, 1984; Brazelton & Nugent, 2011). The purpose of this tool was to assess the individuality of the infant within the interactional process. This state scale was derived both from Dr. Brazelton's clinical experiences and from the existing state systems of Prechtl and Beintema (1968) and Thoman (1975). Brazelton's state scoring system consists of six states: deep sleep, light sleep, drowsy, alert, considerable motor activity, and crying. During the administration of the NBAS, this scoring system is used to identify predominant states, state transitions, and the quality of the alertness. However, it can also be used for scoring sleep–wake states during other situations. By 1983, more than 100 papers had been published using the NBAS and Brazelton's state scale (Brazelton, 1984), and many more have been published since then.

Brazelton's state scoring system has a number of advantages that make it the scoring system of choice for clinicians and also useful for researchers. This state system is easy to learn because the differences between the states are fairly obvious and there are only six states. Because of the widespread use of Brazelton's state scoring system, individuals experienced with this scale are located in virtually every part of the United States. In addition, there are reliability training centers located throughout the country for those who want to use the entire NBAS or plan to use the state scoring system in research. Thus, obtaining training in this scoring system is relatively easy. Finally, most researchers and experienced clinicians are familiar with the state definitions from this scale so that findings of sleeping and waking observations made with this scoring system are readily understood.

On the other hand, this state scoring system does have some limitations for use in research. First, because of the small number of states, it is not always sensitive enough to identify differences between normal full-term infants and infants with perinatal complications. Moreover, the NBAS state scoring system is appropriate for use only with infants between 36 and 44 weeks' GA. The sleeping and waking states of infants born before 36 weeks' gestation and those born after 44 weeks' gestation will not be completely captured with this system. For example, older infants frequently are motorically active and alert during play, but in Brazelton's system, alertness is scored only when the infant is motorically quiet. Young preterm infants are frequently unable to make much sound when crying; thus, their cry periods would be scored as considerable motor activity.

Thoman's State Scoring System. Evelyn B. Thoman was a psychobiologist who worked at the University of Connecticut. Although trained as an experimental psychologist to work with animals, she became interested in the interactions between human infants and their mothers when she went to work with Dr. Anneliese Korner at Stanford University in 1969 and studied them for the rest of her career. She developed her first state scoring system in 1975 (Thoman, 1975) based on the work of Wolff (1966) and Korner (1972). Although some researchers continue to use this system today, it has undergone considerable revision (Thoman, 1990). The Thoman state scoring system consists of 10 sleeping and waking states: alert, nonalert waking activity, fuss, cry, daze, drowse, sleep–wake transition, active sleep, active–quiet transitional sleep, and quiet sleep. Dr. Thoman and others have shown that both acceptable interrater reliability and test–retest reliability can be obtained with her system (Holditch-Davis & Edwards, 1998a; Holditch-Davis, Scher, Schwartz, & Hudson-Barr, 2004). Predictive validity is demonstrated by evidence that early sleeping and waking behaviors scored on Thoman's scale are related to later developmental outcome (Holditch-Davis, Belyea, & Edwards, 2005; Thoman, Denenberg, Sieval, Zeider, & Becker, 1981).

Thoman's state scoring system has a number of advantages. The documented reliability and validity of this system is of value to researchers. The sleeping and waking states are differentiated enough that they can be used with infants with perinatal complications (Holditch-Davis, Scher, Schwartz, & Hudson-Barr, 2004; Thoman, Holditch-Davis, Graham, Scholz, & Rowe, 1988). This system has been used with preterm infants (Holditch-Davis, Scher, Schwartz, & Hudson-Barr, 2004; Liaw et al., 2013; Lorenz et al., 2017) and with infants older than 1 month after term (Holditch-Davis, Miles, & Belyea, 2000). The states in this system can also be combined when an investigator does not need such fine discriminations.

This scoring system has two disadvantages. A 10-state system is somewhat more difficult to learn than a six-state system because it requires subtler discriminations. However, individuals experienced in using a six-state system, such as Brazelton's, can readily learn this system. Also, because this state scoring system is not as widely used as Brazelton's, obtaining training in its use is more difficult.

Als State Scoring System. Heidelise Als is a psychologist working at Harvard Medical School with Dr. Brazelton's colleagues. For a number of years, she has worked with them to modify the NBAS (Brazelton, 1984) to make it more appropriate for use with premature infants. The APIB is administered in much the same way as the NBAS, but the infant's behavior is scored in much greater detail so as to quantify not only the infant's skills but also the infant's reactivity and stress in response to environmental stimulation (Als et al., 1982; Pressler & Hepworth, 2002). Like the NBAS, the APIB is best administered to infants between 36 and 44 weeks' GA, but the observational portion of the tool can be used with younger preterm infants (Als, 1986). The state scale from the NBAS has been expanded into a 13-state system by subdividing each of the six states so that the immature and unclear sleeping and waking states of preterm infants can be more adequately described. These 13 states are very still deep sleep, deep sleep, light sleep, "noisy" light sleep, drowsy with more activity, drowsy, awake and quiet, hyperalert, bright alert, active, considerable activity, crying, and lusty crying. The state subscale of the APIB has been shown to differentiate between premature and full-term infants after term (Als, Duffy, & McAnulty, 1988; Mouradian, Als, & Coster, 2000) and to correlate with electrophysiologic measures of brain activity (Duffy, Als, & McAnulty, 1990). In addition, the APIB and the state subscale are used to provide assessments that are the basis for planning individualized interventions as part of the NIDCAP (Als, 1986; Als et al., 1986; Pressler & Hepworth, 2002).

The Als state scoring system has a number of advantages and disadvantages for clinicians and researchers. First, a 13-state system is more difficult to learn than a six-state system such as Brazelton's (Brazelton & Nugent, 1995). However, since the Als system was developed from the Brazelton states, individuals familiar with the Brazelton system should have no difficulty learning it, and when the complexity of the 13 states is not needed they can be collapsed to the six states from the NBAS. Second, inasmuch as

the APIB, like the NBAS, was never intended for use with infants older than 1 month after term, the state scale may not adequately capture the states of older infants.

Anderson's Behavioral State Score (ABSS). Gene Cranston Anderson is a doctorally prepared nurse researcher who worked at Case Western Reserve University in Cleveland, Ohio. She has long been interested in interventions that keep mother and infant together after birth, reduce infant crying, and promote feeding. She developed a 12-state scoring system, the ABSS, to be used with preterm infants based on her own observations of these infants (Anderson, 1999) and on the work of Parmelee and Stern (1972). Parmelee was one of the contributors to the UCLA state manual (Anders et al., 1971). The ABSS consists of very quiet sleep, quiet sleep with irregular respirations, restless sleep, very restless sleep, drowsy, quiet awake, alert inactivity, restless awake, very restless awake, fussing, crying, and hard crying. The states are arranged so that there is a linear relationship between the states and HR and energy consumption, with the states with the lowest numbers having the lowest mean HRs. The ABSS has been used to show the effects of noise-reducing earmuffs (Khalesi, Khosravi, Ranjbar, Godarzi, & Karimi, 2017) on preterm infant state patterns.

As with the other scoring systems, the ABSS has a number of advantages and disadvantages for clinicians and researchers. Because the ABSS was designed for use with preterm infants, the utility of this scale for full-term infants and older infants is unknown, although its similarity to other state scoring systems suggests that it should be applicable for healthy full-term newborn infants. The ABSS may also be difficult to learn because of the complexity of 12 states. As Table 31.2 illustrates, the sleep states in this system differ markedly from the sleep states defined in other state scoring systems; so, this is not a good scoring system to use if one is primarily interested in studying sleep states and wants to compare findings with other studies. Finally, the linear relationship between the states in this system and heart rate may make it the ideal choice for researchers who are primarily interested in studying the energy consumption of infants. However, this feature means the ABSS has a very different theoretical basis than the other state scales. The other state scoring systems differentiate among states based on qualitatively different aspects of the infant's behavior, but the ABSS emphasizes quantitative differences among the states, although more recently Anderson emphasized qualitative differences between states.

Automated Scoring of States. Because scoring sleeping and waking from EEG or behavioral observations is time intensive, automated methods of scoring sleep–wake states are being developed for research and clinical use. One method often mentioned is video recording. Although video recording is often used for behavioral scoring (Cremer et al., 2016) or along with EEG (Axelin, Kirjavainen, Salanterä, & Lehtonen, 2010; dos Santos, Khan, Rocha, & Nunes, 2014), it does not reduce the time involved because the video recordings need to be scored.

A method currently being used for EEG is amplitude-integrated EEG (aEEG) monitoring, in which EEG traces are digitally recorded for visual scoring and calculation of signal parameters. This technique is currently in use for both research and clinical care (Axelin et al., 2010; El-Dib, Massaro, Glass, & Aly, 2014; Vesoulis et al., 2015). Also, new criteria for scoring sleeping and waking from aEEG are currently being developed (Dereymaeker et al., 2017; Koolen et al., 2017; Palmu, Kirjavainen, Stjerna, Salokivi, & Vanhatalo, 2013).

For behavioral scoring of state, several different methods of scoring are currently in use in research. HR variability has been used to score sleep–wake states (Werth, Atallah, et al., 2017; Werth, Long, et al., 2017). Several researchers have scored sleeping and waking using actigraphy, an activity recorder that is placed on the infant's arm or leg (Gertner et al., 2002; Lan et al., 2018). Although commercial scoring algorithms are available, actigraphy cannot reliably differentiate between active sleep and quiet sleep in preterm infants or full-term newborn infants, and it sometimes confuses waking and active sleep (Rioualen et al., 2015; Sadeh, Dark, & Vohr, 1996). Thus, it should only be used for scoring sleeping versus waking, and then with caution.

Several researchers have developed systems for scoring sleeping and waking from body movements and respiration. Thoman and Glazier (1987) developed a computerized system for scoring sleeping and waking in full-term infants from movements and respiration. They validated this system against direct observation of state. Brandon and Holditch-Davis (2005) validated a semiautomatic method of scoring sleeping and waking from respiratory patterns, motility, and electro-oculography in preterm infants. They showed this system scored state similar to direct observation. Although these systems are promising, they have only been used in research to date.

Description of Individual States. Because the definitions of sleep–wake states are so similar among these scoring systems (see Table 31.2), it is possible to describe in general the sleeping and waking states displayed by infants. For clarity's sake, generic state names are used in all further descriptions. When they are not available, the state names from the Thoman system are used. Each sleeping and waking state is made up of a different constellation of behaviors and serves a different function for the infant. Physiologic functioning is also different in each of these states.

Infants are most responsive to the environment when in the waking states, and, in particular, when alert. When the infant is alert, the eyes are open and scanning. Motor activity is typically low, particularly in full-term newborns, but premature infants and infants older than 1 month after term may be motorically active. Alertness is the state in which the infant exhibits focused attention on sources of stimulation (Brazelton & Nugent, 1995). Thus, this is the best state in which to test reflexes (Prechtl & Beintema, 1968). Alertness has been suggested to be the optimal state for feeding (Griffith, Rankin, & White-Traut, 2017; White-Traut, Berbaum, Lessen, McFarlin, & Cardenas, 2005). This state is also the one in which infants are most receptive to interactions with their parents and other adults. Yet alertness rarely occurs in the preterm period (Holditch-Davis & Edwards, 1998a) and occurs relatively infrequently during the first month after term, only about 10% to 15% of the total day (Colombo & Horowitz, 1987).

Crying, another waking state, serves a communication function. However, the meaning of cries differs in different situations and may depend on their intensity (Fuller, 1991). Although crying that occurs when the infant is alone may elicit parental attention, crying that occurs during social exchanges may actually disrupt the parent–infant relationship. In full-term infants, crying during social interactions is related to the overall amount of maternal stimulation and to consistency in the patterning of maternal activities over weeks (Acebo & Thoman, 1995; Thoman, Acebo, & Becker, 1983). Studies have indicated that the higher the HR, the greater the energy consumption of the infant (Woodson, Field, & Greenberg, 1983). In addition, this state is associated with decreased oxygenation in the bloodstream (Levesque, Pollack, Griffin, & Nielsen, 2000) and brain (Brazy, 1988).

The final waking state, nonalert waking activity, is characterized by periods when the infant is motorically active but not alert or crying. Usually the infant's eyes are open. One study of

nonalert activity found that excess amounts of this state in full-term infants were associated with inconsistency in the patterning of states over weeks (Becker & Thoman, 1982), and, in turn, inconsistency in state patterning was related to poor developmental outcome (Thoman et al., 1981). Premature infants, after term, exhibit elevated levels of this state (Holditch-Davis & Thoman, 1987) and are known to be at increased risk of poor developmental outcome (Adams-Chapman et al., 2018; Marlow, Wolke, Bracewell, & Samara, 2005; Mwaniki, Atieno, Lawn, & Newton, 2012; M. C. Sullivan, Msall, & Miller, 2012). However, whether there is a relationship between these findings is unknown.

The states transitional between sleeping and waking have rarely been the focus of studies. In fact, the Prechtl scoring system omits them altogether on the grounds that they are not true states but just transitions between states (Prechtl & Beintema, 1968). However, newborn infants, both term and preterm, actually spend significant amounts of time in them, ranging from about 6% of the day at 29 weeks' GA to 14% in the first month after term (Holditch-Davis, 1990; Holditch-Davis & Thoman, 1987). Thoman (1990) describes three states transitional between waking and sleeping: drowse, when the infant is quiet and appears sleepy with eyes opening and closing slowly; daze, when the infant is quiet with eyes that are open but dazed in appearance; and sleep–wake transition, when the infant exhibits mixed signals of waking and sleeping, is motorically active, and may appear to be waking up. Drowse and daze typically occur in the midst of periods of waking or as the infant is falling asleep. Sleep–wake transition typically occurs at the end of sleeping as the infant is awakening but may also occur in the middle of sleep, particularly in premature infants. Drowse, daze, and sleep–wake transition are often combined in research reports. However, studies have indicated that these states have different patterns of correlations with other states (Thoman, Holditch Davis, & Denenberg, 1987). During the first month after term, premature infants have been found to spend significantly more time in sleep–wake transition and less time in drowse or daze than full-term infants (Holditch-Davis & Thoman, 1987). If these three states had been combined, these differences would have been missed. In addition, hospitalized preterm infants spend more time in sleep–wake transition when they are with nurses rather than parents, but do not differ in the amount of drowsiness that occurs with these different caregivers (Miller & Holditch-Davis, 1992). During kangaroo mother care, infants show less sleep–wake transition than when alone in their incubators (Lorenz et al., 2017). They also exhibit more sleep–wake transition and less drowsiness during procedural care than during feeding and changing (Brandon, Holditch-Davis, & Belyea, 1999).

There are two major sleep states—active sleep and quiet sleep—although some state systems define a transitional state between them. In active sleep, the infant's respiration is uneven and primarily costal in nature. Sporadic motor movements occur, but muscle tone is low between these movements. Most behaviors, including hiccups, yawns, jitters, negative facial expressions (frowns and grimaces), and large movements, are less frequent in active sleep than waking but more frequent than in quiet sleep, but startles and jerks occur most frequently in active sleep (Holditch-Davis, Brandon, & Schwartz, 2003). The most distinct characteristic of active sleep is REMs that occur intermittently.

Active sleep is the most common state from birth throughout infancy, but it makes up only about 20% of sleep in adults. Because of this dramatic developmental decrease and the frequent movements seen in infants during active sleep, many clinicians think of active sleep as a disorganized and primitive state. Surprisingly, this state has relatively recent phylogenetic origins, occurring only in birds and mammals. Thus, it has been hypothesized to be necessary for brain development (Del Rio-Bermudez & Blumberg, 2018; Roffwarg, Muzio, & Dement, 1966). This hypothesis has received support in full-term infants (Denenberg & Thoman, 1981). In studies of infant animals, prolonged deprivation of active sleep altered brain functioning, resulting in hyperactivity, distractibility, and altered sexual performance (Mirmiran, 1986). Metabolic rates are higher in active than in quiet sleep (Heraghty et al., 2008). Inasmuch as respiratory patterns are relatively unstable in active sleep (Elder, Larsen, Galletly, & Campbell, 2010; Holditch-Davis, Scher, & Schwartz, 2004) and oxygenation is lower and more variable (Ross & Rosen, 2014), the large amount of active sleep seen in young preterm infants (dos Santos et al., 2014; Holditch-Davis, Scher, Schwartz, & Hudson-Barr, 2004) may contribute to their respiratory difficulties.

The other sleep state, quiet sleep, is characterized by a lack of body movements and the presence of regular respiration. A tonic level of motor tone is maintained in this state. Most behaviors, including hiccups, yawns, mouth movements, jitters, negative facial expressions, and large movements, are less frequent in quiet sleep than in waking or active sleep; the exception is sighs, which occur most frequently in quiet sleep (Holditch-Davis et al., 2003). The major purpose of quiet sleep seems to be rest and restoration. This state has been hypothesized to be necessary for healing (Adam & Oswald, 1984). Quiet sleep may also be needed for growth because it is in this state that growth hormone is secreted in adults. However, a study of full-term infants did not find any relationship between growth hormone secretion and quiet sleep (Shaywitz, Finkelstein, Hellman, & Weitzman, 1971). Oxygenation is higher during this sleep state (Ross & Rosen, 2014) and respiration more regular (Elder et al., 2010; Holditch-Davis, Scher, Schwartz, & Hudson-Barr, 2004). Thus, quiet sleep may be beneficial for infants with respiratory problems.

The amount of quiet sleep is also very sensitive to the environment. Infant stimulation studies, for example, have found that quiet sleep is the state most likely to be increased by vestibular and kinesthetic interventions (Ingersoll & Thoman, 1994; Johnston, Stremler, Stevens, & Horton, 1997; Lorenz et al., 2017). The stimulation provided by routine nursing care, on the other hand, results in significantly less quiet sleep than times when the preterm infant is undisturbed (Brandon et al., 1999), and the amount of this state is further reduced when the infant experiences painful or uncomfortable procedures (Holditch-Davis & Calhoun, 1989). Thus, this is the state most likely to be affected by the NICU environment.

Effect of Physiologic Parameters on State. Physiologic functioning varies in different states, and abnormalities in physiologic functioning can alter the sleeping and waking of infants. This discussion focuses on the interrelationship of sleeping and waking and five areas of physiologic functioning of interest to neonatal nurses—illness, the CNS, circulatory system, respiration, and weight gain.

Perinatal Illness. The state patterns of infants who experienced perinatal complications may differ markedly from the state patterns of healthy full-term infants. SGA full-term infants, for example, have more disorganized sleep (more active sleep without REMs) than healthy full-term infants (Watt & Strongman, 1985). At 2 weeks of age, SGA preterm infants had abnormal EEG scores more often and displayed sleep–wake cycling less frequently than average for gestational age (AGA) preterm infants (Schwindt et al., 2015). At 1 month, SGA preterm infants have lower delta percentage on EEGs than AGA full-term and preterm infants and higher theta, alpha, and beta power. Also, preterm infants born to mothers with preeclampsia have less quiet sleep than other preterm infants (Topcuoglu, Kolsuz, Gursoy, Ovali, & Karatekin, 2016).

The sleep of premature infants after term differed from that of full-term infants of the same corrected ages, in that there is a lower total amount of sleep, longer episodes of quiet sleep, more body movements, more frequent REM episodes, and a lower correlation among the various behavioral criteria of the sleep states (Holditch-Davis & Thoman, 1987; Watt & Strongman, 1985). Premature infants show day–night differentiation in their sleeping and waking patterns at the same or an earlier postmenstrual age than full-term infants (C. Guyer et al., 2015; Whitney & Thoman, 1994). In addition, their EEG patterns differ from those of full-term infants. Premature infants display longer bursts during trace alternans, earlier sleep spindle appearance, more immature EEG patterns, poorer phase stability for EEG frequencies, and more transitional sleep (Karch et al., 1982; Nunes, Khan, Gomes Filho, Booij, & da Costa, 2014). Premature and full-term infants also differ on architectural, phasic, continuity, spectral, and autonomic measures (M. S. Scher, Johnson, Ludington, & Loparo, 2011; M. S. Scher, Sun, Steppe, Guthrie, & Sclabassi, 1994). In particular, premature infants display shorter sleep state cycles, less quiet sleep, more arousals in quiet sleep, and less REM in active sleep (Scher et al., 2011). However, some researchers have found that children born prematurely have similar rates of sleep problems from 5 months through for corrected age as full-term infants (Wolke, Söhne, Riegel, Ohrt, & Osterlund, 1998), whereas others have found that 2-year-old prematurely born children at 2 years were more restless during the night (Caravale et al., 2017).

The ways in which the waking states differ between full-term and premature infants of similar postmenstrual ages are less well established. Over prolonged observation periods, premature infants exhibited more alertness and nonalert waking activity and less drowsiness than full-term infants (Holditch-Davis & Thoman, 1987).

The severity of illness that the infant experiences during the perinatal period has relatively small additional effects on sleeping and waking. In general, critical illness has immediate effects on sleeping and waking patterns, but these effects disappear after the infant recovers as long as there are no neurologic complications and as long as infants are observed at the same ages corrected for GA at birth. Karch et al. (1982) studied healthy and ill preterm infants at comparable ages and found that ill infants exhibited more quiet sleep, more indeterminate sleep, and less wakefulness. Palmu et al. (2013) found that ill preterm infants receiving mechanical ventilation had fragmented sleep states. Lan, Yin, Chen, Chang, and Liaw (2017) found that infants with more severe illnesses had more frequent sleep and wake bouts. Respiratory treatments affect infant sleep: the longest sleep cycle of mechanically ventilated preterm infants was shorter than that of nonventilated infants (Curzi-Dascalova, 1992), and infants receiving high-flow nasal cannula oxygen slept less and were more active than infants receiving nasal continuous positive airway pressure (CPAP; Collins, Barfield, Davis, & Horne, 2015). Holditch-Davis and Hudson (1995) used changes in sleep–wake states to identify a wide variety of acute medical complications in preterm infants, including hydrocephalus, sepsis, and cold stress. At term, preterm infants with medical complications showed lower sleep cyclicity scores than healthier preterm or term infants (Feldman, 2006) and at 18 months corrected age, infants with more severe neonatal illness showed less loud snoring and restless sleep (Wang, Difiore, Martin, Rosen, & Hibbs, 2013).

Studies of infants who have recovered from their illnesses have found fewer differences. High and Gorski (1985) did not find any differences in the sleeping and waking patterns of convalescent premature infants differing in the severity of their previous illness. Likewise, Holditch-Davis (1990) found that the only difference in the development of sleeping and waking states in convalescent preterm infants was that more severely ill infants showed less fussing and somewhat poorer organization of quiet sleep. However, Holditch-Davis, Scher, Schwartz, and Hudson-Barr (2004) found that longer mechanical ventilation was associated with more active sleep and less active sleep without REMs, and that infants with lower birth weights had more regularity of respiration in quiet sleep. On the other hand, Brandon, Holditch-Davis, and Winchester (2005) found that longer mechanical ventilation was associated with less active sleep. In addition, scores on the NBAS state scale did not differ significantly between sick and healthy full-term infants at the time of hospital discharge (Holmes et al., 1982).

Infants with CLD are more likely than other premature infants to have oxygen desaturations when sleeping (Barbeau & Weiss, 2017). Yet, how this illness affects sleeping and waking patterns is unclear. Holditch-Davis and Lee (1993) compared preterm infants with and without CLD from 32 to 36 weeks' postmenstrual age on sleeping and waking during 4-hour observations in the intermediate care unit. The only difference between the infants with and without CLD was that infants with CLD had more irregular respiration in quiet sleep. Although many clinicians believe that infants with CLD are more sensitive to stimulation, there were also no differences in sleeping and waking when the infants with and without CLD were with caregivers (Holditch-Davis, 1995). However, at 36 weeks' postmenstrual age, preterm infants with CLD had fewer periods of quiet sleep per hour and their EEG patterns differed as compared to preterm infants without this complication (Sommers, Tucker, & Laptook, 2011). At term age, premature infants with CLD were found to have less active sleep, more frequent arousals, and more frequent body movements in sleep than premature infants who never experienced any respiratory illnesses and performed more poorly on the interactive and motor clusters of the NBAS (Myers et al., 1992).

Treatments for perinatal illnesses also may affect the sleeping and waking states of preterm infants. For example, supplemental oxygen was associated with increased quiet sleep and total sleep time (Simakajornboon, Beckerman, Mack, Sharon, & Gozal, 2002). One study of preterm infants between 28 and 32 weeks' postmenstrual age found that oxycodone was associated with a reduction in active sleep and an increase in sleep onset in quiet sleep as compared to a placebo, oral glucose, or swaddling by parents (Axelin et al., 2010). Prenatal magnesium sulfate affected the organization of sleep states leading to dysmaturity (a combination of accelerated and delayed state organization), whereas antenatal steroids had no effect (Black, Holditch-Davis, Schwartz, & Scher, 2006). Preterm infants whose mothers received antenatal phenobarbital did not differ in HR or sleep–wake states in the first 3 days of life from infants not receiving the medication, suggesting that the antenatal dosage was not sedating (McCain, Donovan, & Gartside, 1999).

Neurologic System. Because sleeping and waking states are assumed to reflect the underlying activation of the CNS, it is not surprising that a close relationship exists between sleep–wake states and CNS functioning. Four factors illustrate this interrelationship. First, sleeping and waking exhibit a large amount of development in the first year of life, the time of the most rapid CNS development. Sleeping and waking states affect neurologic responses. Infants with neurologic abnormalities exhibit abnormal sleeping and waking patterns. Finally, sleeping and waking states can be used to predict developmental outcome.

Development of Sleeping and Waking States. Infants exhibit definite developmental changes in their sleeping and waking state patterns throughout the first year of life. The age at which

sleep–wake states first appear is unknown. Studies of preterm infants have found that by 24 weeks' GA, cycling between waking and sleeping can be identified by EEG in some preterm infants (Pavlidis, Lloyd, Mathieson, & Boylan, 2017). By 24 to 27 weeks' GA (the earliest ages studied), infants exhibit distinct waking and sleeping states (Holditch-Davis, Scher, Schwartz, & Hudson-Barr, 2004; Palmu et al., 2013; M. S. Scher, Johnson, & Holditch-Davis, 2005). However, before 30 weeks' GA, the various behaviors associated with sleep and waking—eye movements, body movements, respiration, and muscle tone—are not well coordinated; not until at least 36 weeks' GA do preterm infants exhibit the same degree of correlation between these parameters as do full-term infants (Curzi-Dascalova, Peirano, & Morel-Kahn, 1988; dos Santos et al., 2014). Studies of sleeping and waking states in fetuses conducted using observations made during ultrasound examinations have had similar findings (DiPietro, Hodgson, Costigan, Hilton, & Johnson, 1996).

Infants exhibit greater amounts of active sleep and indeterminate states during the preterm period and lower amounts of waking states than after term (Holditch-Davis, Scher, Schwartz, & Hudson-Barr, 2004; Lan et al., 2017). Active sleep occupies as much as 60% to 80% of the day for young preterm infants (Barbeau & Weiss, 2017; Holditch-Davis & Edwards, 1998a; Holditch-Davis, Scher, Schwartz, & Hudson-Barr, 2004), although one study found that preterm infants spent more time in quiet sleep in the morning (Llaguno et al., 2015). The major developmental change during the preterm period is a decrease in the amount of sleep due to a decrease in active sleep (Holditch-Davis, Scher, Schwartz, & Hudson-Barr, 2004; Ingersoll & Thoman, 1999; Lan et al., 2017). In addition, quiet sleep and waking states, especially crying, increase (Barbeau & Weiss, 2017; Cremer et al., 2016; Holditch-Davis, Scher, Schwartz, & Hudson-Barr, 2004). The organization of the sleep states, as measured by the percentages of the state with typical state criteria, by the correlation between criteria, and by the presence of definite sleep state cycles, also increases throughout the preterm period (Barbeau & Weiss, 2017; Feldman, 2006; Holditch-Davis, Scher, Schwartz, & Hudson-Barr, 2004; Soubasi et al., 2009). EEG criteria also change with age over the preterm period: maximum amplitude of EEG decreases; minimum amplitude increases; and smooth delta waves, delta brushes, and theta bursts decrease (Vesoulis et al., 2015). The mean duration and frequency of episodes of each state also change over the preterm period: quiet waking, active waking, and sleep–wake transition episodes occurred more frequently than active waking and quiet sleep, but length of these periods increased over age (Holditch-Davis & Edwards, 1998b; Ingersoll & Thoman, 1999). These changes may be affected by gender as male preterm infants exhibited less active sleep, more drowsiness, and more waking than females (Foreman, Thomas, & Blackburn, 2008).

The sleeping and waking states of infants in the first month after term differ dramatically from those of infants in the preterm period. Healthy full-term neonates sleep about 13.5 hours a day (Thomas & Foreman, 2005), have a sleep–wake cycle of about an hour in length, and spend more sleep time in active sleep (Korotchikova, Stevenson, Livingstone, Ryan, & Boylan, 2016). Slightly higher amounts of sleep states occur at night (Thoman & Whitney, 1989; Whitney & Thoman, 1994). Waking states make up the rest of the day, with alertness (14%) and drowsiness (13%) being the most common (Holditch-Davis & Thoman, 1987).

The major developmental trends exhibited by full-term infants in the first month are a decrease in active sleep and an increase in the amount of alertness (Denenberg & Thoman, 1981; Kohyama & Iwakawa, 1990). Moreover, the mean lengths of episodes of the sleep states change, with active sleep decreasing and quiet sleep increasing (Thoman & Whitney, 1989). Similar trends occur for premature infants during this period (Mirmaran, Baldwin, & Ariagno, 2003; Whitney & Thoman, 1994). In addition, both full-term and premature infants begin to show entrainment to a day–night schedule of sleeping and waking by about a month after term (Shimada et al., 1999).

Sleeping and waking states continue to develop throughout the first year. Waking periods become longer and more consolidated (Holditch-Davis, Tesh, Burchinal, & Miles, 1999; Louis, Cannard, Bastuji, & Challamel, 1997), and night wakings decrease (Mäkelä et al., 2018). The infant spends an increasing proportion of wakefulness in the alert state. The amount of time spent crying decreases (Michelsson, Rinne, & Paajanen, 1990; St. James-Roberts & Plewis, 1996). In addition, total sleep time decreases, with almost all of this decrease due to a decrease in active sleep time (Holditch-Davis et al., 1999; Louis et al., 1997; Mäkelä et al., 2018). The amount of quiet sleep remains the same or increases from term age on; thus, by about 6 months of age, the amount of quiet sleep exceeds the amount of active sleep (Louis et al., 1997). In addition, the number of sleep episodes decreases and becomes consolidated primarily into nighttime, although most infants continue to exhibit some amount of night waking (Ottaviano, Giannotti, Cortesi, Bruni, & Ottaviano, 1996; A. Scher, 1991). By 1 year, the infant is taking about two daytime naps (Weissbluth, 1995) and sleeping about 10 to 12 hours through the night. Prematurely born infants may display shorter night sleep, more activity during the night, and more sleep problems than full-term infants (Asaka & Takada, 2010; Huang, Paiva, Hsu, Kuo, & Guilleminault, 2014).

The nature of these changes depends somewhat on the caregiving environment. Thus, breastfed infants exhibit less total sleep, longer sleep latency, more fragmented sleep, more non-REM sleep, and shorter duration of REM sleep than formula-fed infants (Figueiredo, Dias, Pinto, & Field, 2017; Schwichtenberg & Poehlmann, 2009; Tikotzky et al., 2010), but not at 2 weeks (Figueiredo et al., 2017). Also, 2-week-old and 6-month-old full-term infants with depressed mothers took longer to fall asleep and had more disrupted sleep than infants of nondepressed mothers (Armitage et al., 2009).

Other developmental changes during the first year affect the organization of sleep. The cycling between active and quiet becomes more consistent over the first few months. Many preterm infants display hour-long sleep cycles by 36 weeks' postmenstrual age (Borghese, Minard, & Thoman, 1995). The sleep states also develop the EEG patterns typical of adults. By 3 months of age, the EEG stages within quiet sleep can be identified, and this state can now be called non-REM sleep (Ellingson & Peters, 1980).

Neurologic Responses. Infants exhibit different neurologic responses in different sleeping and waking states. The magnitude of neurologic reflexes is known to differ greatly in different states (Prechtl & Beintema, 1968). Therefore, standardized infant assessments and neurologic examinations specify which states are optimal for testing each reflex (Brazelton & Nugent, 1995; Prechtl & Beintema, 1968). The amplitude, waveform, and latency of visual evoked potentials are different in different sleeping and waking states, with the greatest differences being between sleep and waking (Apkarian, Mirmiran, & Tijssen, 1991).

Neurologic Problems. The state patterns of infants with neurologic insults differ markedly from those of healthy infants. Infants with Down syndrome have been found to spend more time awake and to have abnormally long periods of quiet sleep (Prechtl, Theorell, & Blair, 1973). Premature infants with IVH have been found to be more likely to lack sleep–wake cycles than healthier preterm infants (Olischar, Klebermass, Waldhoer, Pollak, & Weninger, 2007). Full-term infants with hyperbilirubinemia show decreased

amounts of wakefulness (Prechtl et al., 1973). As compared to full-term infants with only mild bilirubin elevations, infants with moderately elevated bilirubin values exhibited significantly lower scores in state regulation and range on the NBAS, and exhibited minor neurologic abnormalities as shown by increased latency of brainstem auditory evoked potentials (Vohr et al., 1990). On the other hand, very preterm infants on phototherapy did not differ on the amount of quiet sleep from very preterm infants not on phototherapy (Cremer et al., 2016). Abnormal cry patterns have been found in infants who have neurologic injuries, hyperbilirubinemia, or are at risk for sudden infant death syndrome (SIDS; Corwin et al., 1995). Greater EEG quiet sleep and decreased delta power in quiet sleep were associated with worse neurologic examinations of infants at risk for seizures (Shellhaas, Burns, Barks, & Chervin, 2014). Infants (5–24 months of age) with congenital Zika syndrome showed less total sleep and more night waking than healthy infants (Pinato et al., 2018).

In addition, infants exposed prenatally to drugs or alcohol exhibit abnormalities in their state patterns, possibly as the result of neurologic insults caused by the drugs. For example, alcohol-exposed infants exhibit sleep disruptions and abnormal cries (Nugent, Lester, Greene, Wieczorek-Deering, & O'Mahony, 1996). Preterm infants whose mothers smoked prenatally had more active sleep, more waking after sleep onset, more motor activity in sleep, and altered peripheral chemoreceptors (decreased baseline activity in active sleep and increased response time in quiet sleep; Stéphan-Blanchard, Chardon, et al., 2010; Stéphan-Blanchard, Telliez, et al., 2008). Infants exposed to marijuana exhibit a decrease in quiet sleep time (M. S. Scher, Richardson, Coble, Day, & Stoffer, 1988). Methadone-exposed infants exhibit abnormal cries with short first expirations and are more irritable and less able to sustain a high-quality alert state (Huntington, Hans, & Zeskind, 1990; Jeremy & Hans, 1985). Infants experiencing opiate withdrawal exhibit more waking, more sleep fragmentation, and less quiet sleep (O'Brien & Jeffery, 2002). Infants who were exposed to cocaine or opiates during pregnancy showed more alertness and less quiet sleep than nonexposed infants (White-Traut et al., 2002). Infants who were prenatally exposed to cocaine showed less active sleep and more indeterminate sleep; they also showed less orientation and poorer state regulation, including more jitters, high-pitched cries, and hyperalertness, than drug-free infants (Bauer et al., 2005; Regalado, Schechtman, Del Angel, & Bean, 1995). On the other hand, Woods, Eyler, Behnke, and Conlon (1993) did not find any differences on the NBAS between cocaine-exposed and drug-free infants.

Prediction of Developmental Outcome. Finally, the organization of sleeping and waking, as indicated by individual state criteria or the overall patterning of states, can be used to predict the developmental outcome of infants. Greater amounts of quiet sleep in the preterm period relate to better alertness and orientation, less irritability, and better orientation to inanimate visual and auditory stimulation on the NAPI (Korner & Thom, 1990), an assessment similar to the APIB, at 32 and 36 weeks' postmenstrual age (Brandon et al., 2005). Delayed maturity of EEG patterns of preterm infants was found to be associated with poor neurologic outcome (Ferrari et al., 1992; Hahn & Tharp, 1990), and less mature sleep–wake cycling scores in the preterm period were associated with lower cognitive and motor development between 9 and 18 months corrected age (El-Dib et al., 2014; C.-M. Jiang et al., 2015). Also, in preterm infants, lower EEG energies, especially in active sleep, and prolonged interburst intervals predicted lower neurodevelopmental performance at 12 and 24 months and greater likelihood of death, cerebral palsy, other neurologic problems, or sensory impairments (Thiriez et al., 2015; Wikström et al., 2012). Sleep difficulties at 2 years were related to shorter attention (Caravale et al., 2017). Elevated amounts of intense bursts of REMs and long sleep cycle lengths at 6 months were associated with developmental problems in full-term infants (Becker & Thoman, 1982; Borghese et al., 1995) and low amounts of REMs were associated with lower Bayley mental development scores at 6 months corrected age in preterm infants (Arditi-Babchuk, Feldman, & Eidelman, 2009). Measures of sleep–wake states during the preterm period—including the total amount of sleep, the overall state organization as compared with other infants, predominant pattern of state transitions, and sleep cycle length—have been found to predict Bayley scores at 6 months to 3 years corrected age (Gertner et al., 2002; Holditch-Davis et al., 2005; Weisman, Aderka, Marom, Hermesh, & Gilboa-Schechtman, 2011; Whitney & Thoman, 1993). However, the amount of indeterminate sleep—any period not meeting the criteria for one of the five states defined by Prechtl and Beintema (1968)—in premature infants at term was not related to developmental status at 2 years (Maas et al., 2000). In apparently normal full-term infants, the stability of state patterns in the first month has been found to predict developmental outcome (Thoman et al., 1981). This finding has been replicated in premature infants after term (Whitney & Thoman, 1993) and in siblings of infants who died from SIDS (Thoman et al., 1988).

Circulatory System. Sleeping and waking states affect the infant's circulatory system. Overall, HR is higher in waking than sleeping states (Llaguno et al., 2015). Mean HRs in the two sleep states are very similar, but HR is more variable in active sleep (Elder et al., 2010; Galland et al., 2000); high frequency HR variability increases with age, the low frequency/high frequency ratio decreases, and low frequency blood pressure variability decreases, especially in active sleep (Yiallourou, Witcombe, Sands, Walker, & Horne, 2013). The difference in variability is large enough that it is possible to differentiate between the two sleep states on the basis of HR variability (Werth, Long, et al., 2017). Thus, neonatal nurses need to be aware of the infant's state when determining HR, and routine vital signs probably should not be obtained while the infant is crying.

Sleeping and waking states also affect the infant's circulation. Cerebral blood flow is highest during waking (Greisen, Hellstrom-Vestas, Lou, Rosen, & Svenningsen, 1985). It is significantly higher in active sleep than in quiet sleep in full-term infants (Milligan, 1979), but not in infants less than term age (Greisen et al., 1985). Variability in cerebral blood flow velocity is lowest in quiet sleep, whereas marked fluctuations occur during active waking (fussing and nonalert waking activity; Ramaekers, Casaer, Daniels, Smet, & Marchal, 1989). Blood pressure is slightly higher when the infant is awake than when asleep (Van Ravenswaaij-Arts, Hopman, & Kollee, 1989) and lower in quiet sleep than active sleep (Witcombe, Yiallourou, Walker, & Horne, 2008).

Respiration. The effect of sleeping and waking states on the respiratory system is even greater than on the circulatory system. The nervous system controls of breathing differ in different states (Phillipson, 1978; Ross & Rosen, 2014). During wakefulness, breathing is regulated by metabolic controls, general stimulation from the reticular activating system, and voluntary activities. In quiet sleep, metabolic controls predominate, and maintaining acid–base and oxygen homeostasis is the primary stimulus for breathing. Medullary respiratory center activity varies during active asleep depending on whether the infant is experiencing REMs and motor activity (phasic active sleep) or not (tonic active sleep), indicating that these two types of active sleep include different controls on breathing. During phasic active sleep, behavioral controls similar to the voluntary controls in waking predominate. In tonic active sleep, the major respiratory control results from direct stimulation

of the state in a manner similar to the reticular stimulation of respiration during wakefulness. As a result of these different controls, infants exhibit higher respiratory rates and lower tidal volumes in phasic active sleep than in tonic active sleep (Ross & Rosen, 2014). In addition, the Hering–Breuer reflex is strong in active sleep in preterm infants (Hand et al., 2004).

Respiratory activity responds differently to chemical stimulation in different states. Baseline arterial oxygen and carbon dioxide levels are lower in active sleep than in either waking or quiet sleep (Mok et al., 1988; Ross & Rosen, 2014), possibly because of hypoventilation or ventilation–perfusion inequalities in this state. Arousal in response to hypoxia differs in quiet sleep and active sleep, with some studies finding that it is slower in quiet sleep (Parslow, Harding, Adamson, & Horne, 2004) and others finding it slower in active sleep (Fewell & Baker, 1987). Response to hypercapnia is also different in different states. There is a shift to the right in the carbon dioxide response curve in quiet sleep as compared to waking (E. Cohen, Xu, & Henderson-Smart, 1991; Phillipson, 1978). This response is further reduced in tonic active sleep and is absent in phasic active sleep (C. E. Sullivan, 1980).

As a result of these differing neurologic controls on breathing, a number of respiratory variables in both full-term and preterm infants are influenced by sleep and waking states. Respiration rates are higher and more variable in active sleep (Elder, Campbell, Larsen, & Galletly, 2011; Holditch-Davis, Scher, & Schwartz, 2004). Active sleep has also been shown to result in hypoventilation in preterm infants because of central inhibition of spinal motoneurons (Schulte, Busse, & Eichhorn, 1977) and poor coordination between chest and abdominal muscles (Gaultier, 1990). Thus, paradoxical movements of the chest wall and abdominal muscles during breathing are common during active sleep in preterm infants, and oxygen saturation is somewhat lower (Elder et al., 2011). However, it is not clear whether lung volume is decreased in active sleep in full-term infants. Expiratory volumes and flow rates are larger in waking infants than in sleeping ones (Lodrup, Mowinckel, & Carlsen, 1992).

The frequency of central apnea also differs between the two sleep states. Central apnea rarely occurs during waking. Most studies indicate that brief apneic pauses of less than 20 seconds in length occur more frequently in active sleep than quiet sleep in both full-term and preterm infants (Curzi-Dascalova, Bloch, Vecchierini, Bedu, & Vignolo, 2000; Holditch-Davis, Scher, & Schwartz, 2004; Vecchierini, Curzi-Dascolova, Ha, Bloch, & Gaultier, 2001). However, the frequency of periodic respiration (cyclic breathing alternating with brief apneic pauses) does not appear to differ between the sleep states (Decima, Fyfe, Odoi, Wong, & Horne, 2015; Holditch-Davis, Scher, & Schwartz, 2004; Horne et al., 2018). The mean length of apneic pauses is longer in quiet sleep (Holditch-Davis, Scher, & Schwartz, 2004). In addition, a variety of stresses, including an increase in body temperature and sleep deprivation, have been shown to increase apnea frequency, primarily in active sleep (Gaultier, 1994).

However, it cannot be concluded from these studies that pathologic apneas (apneic episodes longer than 20 seconds and usually associated with bradycardia and hypoxemia) are more common in active sleep because studies rarely included episodes of pathologic apnea. Pathologic apnea is often too rare to permit statistical analyses comparing states (Holditch-Davis, Scher, & Schwartz, 2004). However, Tourneux et al. (2008) found that pathologic apnea with oxygen desaturation was more common in active sleep, whereas the frequency of pathologic apnea without desaturation did not differ between the sleep states. In addition, some association between active sleep and pathologic apnea is suggested by the fact that the methylxanthines, caffeine and theophylline, used to treat this condition are generally found to increase the amount of wakefulness and decrease the amount of sleep in addition to their direct effects on respiration (Brandon et al., 2005; Thoman et al., 1985). On the other hand, Hayes et al. (2007) found decreased waking, brief arousals, and movement bouts with caffeine or theophylline treatment. Infants have also been found to have greater respiration regularity in active sleep during treatment with theophylline and caffeine (Holditch-Davis, Scher, & Schwartz, 2004). Some studies have found that theophylline and caffeine had minimal effects on sleep–wake development (Curzi-Dascalova, Aujard, Gaultier, & Rajguru, 2002; Holditch-Davis & Edwards, 1998a), whereas others found theophylline was related to greater maturity of active sleep–quiet sleep cycles on the EEG (H. J. Lee et al., 2010).

Weight Gain. Studies have found that obesity is related to shorter sleep duration in both adults and children, probably because of a bidirectional relationship in which inadequate sleep increases hunger and excess weight interferes with sleeping (J. Liu, Zhang, & Li, 2012; Meyer, Wall, Larson, Laska, & Neumark-Sztainer, 2012). How early in life this relationship begins is unclear, but recent studies of preterm infants found that sleep patterns in the preterm period (more rapid rate of development of quiet sleep, slower development of active sleep, and lower amounts of active sleep at 29–31 weeks) were associated with a faster rate of weight gain in the preterm period and from 1 to 27 months corrected age and a higher BMI at 1 month (Lan et al., 2017; Winkler et al., 2017). Full-term infants with shorter sleep durations in the first 6 months were more likely to have higher weight-to-length ratios (Tikotzky et al., 2010). These findings suggest that adequate sleep may protect against the development of obesity even in infancy.

Effect of Healthcare Interventions on State. Sleeping and waking states are also affected by the types and timing of stimulation that the infant receives from the environment. Thus, healthcare interventions have the potential to either promote state organization or to disrupt it. The effects of four common nursing interventions—routine NICU care, painful procedures, social interaction, and infant stimulation—on infant sleeping and waking are examined in this section.

Effect of Environmental Stimulation. The hospital provides stimulation that may be inappropriate for the development of premature infants and is likely to result in disorganized sleeping and waking patterns. Research in the 1980s and 1990s indicated that the NICU provided infants with an extremely bright and noisy environment with little diurnal variation and frequent interventions for technical procedures but little positive handling (Duxbury, Henly, Broz, Armstrong, & Wachdorf, 1984; Zahr & Balian, 1995). Similar findings occurred recently in Brazil and the United States (Axelin, Cilio, Asunis, Peloquin, & Franck, 2013; Orsi et al., 2017). The sickest infants actually received the most handling (Zahr & Balian, 1995), even though they lacked the physiologic reserves to cope with it. Recent use of developmental care has probably reduced these effects but some remain. For example, even relatively small increases of 5 to 15 decibels above ambient noise during sleep resulted in arousals for many preterm infants, decreases in respiratory rate in quiet sleep, and decreases in oxygen saturation (Kuhn et al., 2012, 2013).

Premature infants also may become hypoxic in response to virtually any form of stimulation. The severity of the negative physiologic responses to one procedure, endotracheal suctioning, has been related to the infant's state during the procedure (Bernert et al., 1997). Preterm infants who cried during suctioning had greater changes in oxygenation and HR than infants who slept through suctioning. Convalescent infants are handled less than ill

infants and experience social interactions as a greater percent of their care (High & Gorski, 1985).

Several of the aspects of routine NICU care are known to contribute to disruption of infant sleeping and waking patterns. Nursing and medical interventions frequently result in state changes. The frequency of these interventions in the NICU has been found to be as high as five times per hour (Duxbury et al., 1984). Preterm infants change their sleep–wake states about six times per hour, and 78% of these changes are associated with either nursing interventions or NICU noise (Zahr & Balian, 1995). Preterm infants are rarely able to sustain quiet sleep during nursing interventions (Brandon et al., 1999; Liaw et al., 2012) and usually awaken with each intervention. Thus, frequent nursing interventions are particularly likely to reduce the amount of quiet sleep (Liaw et al., 2012). Preterm infants normally spend only a small percentage of their time in waking states (Holditch-Davis, 1990), but this percentage increases significantly when they are with nurses (Brandon et al., 1999; Liaw et al., 2012). Also, developmental changes in the amount of waking occur only over the time infants are with nurses, and the distribution of states differs depending on the nursing activity, with active waking more common and drowsiness less common during more intrusive care (Brandon et al., 1999). On the other hand, preterm infants showed more quiet sleep after nursing interventions than before them (Symanski, Hayes, & Akilesh, 2002), and bathing did not affect sleep–wake patterns (H.-K. Lee, 2002).

Moreover, neonatal nurses and physicians often do not consider infant sleep–wake states and other infant cues when choosing the time for routine interventions. Although two studies found relationships between nursing care and sleeping and waking for groups of preterm infants (Barnard & Blackburn, 1985; Lawson, Turkewitz, Platt, & McCarton, 1985), these results probably represent infant reactions to nursing care or infants conditioned to anticipate regular nursing procedures rather than nurses responding to infant states. Infant activity has been found to decrease after nursing interventions (Blackburn & Barnard, 1985). Gottfried (1985) found that nurses responded to fewer than half the cries of growing preterm infants. Yet, a lack of responsiveness to infant cues may serve to slow the development of stable diurnal patterns of sleeping and waking that have been suggested to be the first task of infancy (Barnard & Blackburn, 1985).

In light of the recommendation by the American Academy of Pediatrics Task Force on Sudden Infant Death Syndrome (2011) that infants be placed on their backs to sleep, the effects of positioning on infant sleep–wake states also need to be considered. Full-term infants in the supine position show greater wakefulness, less quiet sleep, higher cerebral oxygenation levels, lower HRs, higher rates of brief respiratory pauses, and better airway protection during sleep than when prone (Elder et al., 2010; Ghorbani, Asadollahi, & Valizadeh, 2013; Wong et al., 2011). Similar effects on sleeping and waking, HR, and oxygenation have been found in growing preterm infants and in preterm infants with CLD (Ariagno et al., 2003; Bhat et al., 2006; Fyfe et al., 2014; Jarus et al., 2011; Saiki et al., 2009). Arousals occur most frequently when preterm infants are in supine position and least frequently in prone position (Modesto et al., 2016; Richardson & Horne, 2013). In addition, respiration rates are more variable in the supine position in preterm infants, but not in full-term ones (Elder et al., 2011), and arousals are more common (Ariagno, van Liempt, & Mirmiran, 2006). On the other hand, lateral positioning was associated with an increase in quiet sleep (Liaw et al., 2012). Thus, supine positioning is probably not appropriate for preterm infants with respiratory compromise.

However, in growing preterm infants, prone positioning was associated with a reduced ventilatory response to carbon dioxide as compared to supine position (Smith, Saiki, Hannam, Rafferty, & Greenough, 2010). Thus, in preterm infants who are no longer acutely ill, positioning decisions require balancing infant needs for rest and oxygenation with physiologic changes with respiratory maturation and the need to provide an example for parents. Although prone sleeping has decreased after discharge for preterm infants, mothers of preterm infants are still less likely to place their infants in supine position than mothers of full-term infants (Hwang et al., 2016).

Finally, the lighting of the NICU, as discussed earlier in this chapter, contributes to sleeping and waking problems in infants. Lighting in most NICUs is continuous, high level, and fluorescent. The frequency of eye opening and waking states is related to the level of illumination in the NICU; less eye opening occurs when the lights are brightest (Moseley, Thompson, Levene, & Fielder, 1988; Robinson, Moseley, Thompson, & Fielder, 1989). Higher lighting levels are associated with greater wakefulness and less quiet sleep (Orsi et al., 2017). Changes in lighting levels during sleep (even when mild light protection is used) are more likely to result in awakening than periods with constant light levels (Zores et al., 2018). These findings support the common nursing and parental intervention of shading infant eyes with one's hand to elicit alertness. In addition, infants exposed to NICUs that vary the intensity of lighting on a diurnal pattern open their eyes significantly more than those exposed to continuous illumination (Robinson et al., 1989).

In view of the problems with routine NICU care, researchers have attempted to alter this environment to promote better sleeping and waking patterns in infants. When Gabriel, Grote, and Jonas (1981) consolidated nursing care so that convalescent premature infants were disturbed less often, the infants were awake less often and had longer sleep episodes. Fajardo, Browning, Fisher, and Paton (1990) cared for preterm infants in quiet, private rooms with day–night cycles, demand feedings, and social interactions by the nurses. These babies showed an increase in the mean length of active sleep and in the organization of sleep states as evidenced by a decreased number of states. Reducing noise levels in the NICU was associated with greater quiet sleep (Varvara, Effrossine, Despoina, Konstantinos, & Matziou, 2016). Using earmuffs for preterm infants to reduce NICU noise levels was associated with lower mean respiratory rates, HRs, and oxygen saturation and more quiet sleep and less waking states than infants without ear muffs (Khalesi et al., 2017). Cobedded preterm twins spent more time in the same state, spent more time in quiet sleep, and cried less than twins bedded separately (Hayward et al., 2015).

Als and colleagues (1986) developed a system of individualized interventions for preterm infants that included sensitivity to infant cues and careful avoidance of sleep disruptions. Their experimental infants did not exhibit different state patterns compared to the control infants, but the experimental infants did have fewer medical complications and improved performance on the APIB. A replication study found improved state regulation and state stability as measured on the APIB (Buehler, Als, Duffy, McAnulty, & Liederman, 1995). Using a modification of the Als intervention system, Becker, Chang, Kameshima, and Bloch (1991) also found improvements in infant morbidity, but did not find differences in state behaviors on the NBAS at the time of hospital discharge; however, the experimental infants showed higher oxygen saturations, fewer disorganized movements, and more alertness during nursing care than did controls (Becker, Grunwald, Moorman, & Stuhr, 1993). Later studies found that infants receiving the intervention slept more than infants receiving traditional handling (Bertelle et al., 2005). However, still other studies did not find that the Als intervention system had any effect on sleep–wake states, either in

the preterm period or after discharge (Westrup, Hellström-Westas, Stjernqvist, & Lagercrantz, 2002).

A number of researchers altered NICU lighting patterns. Blackburn and Patteson (1991) compared preterm infants in a nursery with continuous lighting with infants in a nursery with lighting that was dimmed at night. Infants in cycled light exhibited less motor activity during the night and lower HRs over the entire day than the control infants. When preterm infants in the intermediate care unit were given four half-hour nap periods a day during which their incubators were covered and they received no nursing or medical procedures, they exhibited less quiet waking and longer uninterrupted sleep bouts than preterm infants without naps (Holditch-Davis, Barham, O'Hale, & Tucker, 1995), and they experienced a more rapid decline in apnea and more rapid weight gain (Torres, Holditch-Davis, O'Hale, & D'Auria, 1997). Reducing light levels in the NICU was associated with greater amounts of quiet sleep (Varvara et al., 2016). Because exposure to light at night for nursing procedures might alter growing preterm infants' biological rhythms, Kaneshi et al. (2016) tested the effects of using red light that the infants could not see. They found no differences in sleep patterns or physical growth between preterm infants exposed to a red light versus a white light. Brandon, Holditch-Davis, and Belyea (2002) compared preterm infants who received care in near darkness with infants who received cycled light. Although there were no differences in state patterns (Brandon et al., 2005), the infants receiving cycled light showed more rapid weight gain (Brandon et al., 2002). In other studies, preterm infants receiving cycled light showed earlier day–night patterning of activity than infants cared for in dim light (Guyer et al., 2015; Rivkees, Mayes, Jacobs, & Gross, 2004). Cycled lighting was associated with less fussing and crying even though no other differences in sleeping or waking were found compared to infants kept in dim lighting (Guyer et al., 2012). However, a fifth study found no differences in sleep or circadian patterns after discharge in infants exposed to dim lighting or cycled lighting (Mirmaran et al., 2003), nor did sleep or neurodevelopmental outcomes differ based on whether the cycled light began at 28 or 36 weeks' postmenstrual age (Brandon et al., 2017). All these findings suggest that neonatal nurses need to examine their routine practices to see if changes could be made to better promote stable sleeping and waking patterns in infants.

Painful Procedures. Infants in intensive care inevitably experience painful procedures. Neonatal nurses need to be alert to the effects of these procedures on infant sleeping and waking states. During painful procedures, infants are more likely to be awake and less likely to be in quiet sleep than during routine nursing care (Fearon, Kisilevsky, Hains, Muir, & Tranmer, 1997; Van Cleve, Johnson, Andrews, Hawkins, & Newbold, 1995). All but the youngest and sickest preterm infants are likely to cry (Johnston, Sherraud, et al., 1999), although the length of time until the cry begins depends on the infant's sleeping and waking state at the beginning of the procedure (Grunau & Craig, 1987). Healthy full-term infants have the longest latency to cry when in quiet sleep, and young, preterm infants who are asleep at the beginning of the procedure and have recently undergone another painful procedure are the most likely to show only a minimal behavioral response to a painful procedure (Johnston, Sherraud, et al., 1999; Stevens, Johnston, & Horton, 1994). Preterm infants tend to stay awake after a painful procedure, but this tendency is not any greater than the tendency to stay awake after routine handling (Holditch-Davis & Calhoun, 1989).

Nursing comfort measures also have the potential to minimize some of the state effects of pain without having negative effects on infant sleep. Yet how frequently practicing nurses actually use them is unclear. Franck (1987) identified nine different comfort measures that nurses reported using to soothe infants who were receiving painful procedures (Chapter 23). To date, only a few of them have been studied. Pacifiers were found to reduce crying and arousal in full-term and preterm infants when given during and after the procedure (Fearon et al., 1997). A sucrose-flavored pacifier was found to be even more effective than a plain pacifier in reducing the amount of crying by full-term and preterm infants during blood drawing and circumcision (Johnston et al., 1997; Johnston, Stevens, et al., 1999). Swaddling has been shown to reduce arousals in sleep and increase REM sleep in full-term infants (Gerard, Harris, & Thach, 2002). Facilitated tucking—a modified form of swaddling in which the infant's arms and legs are contained in a flexed position next to the trunk—was effective in reducing responses to heelsticks (Corff, Seidemanm, Venkataraman, Lutes, & Yates, 1995). Preterm infants who received facilitated tucking during and after heelsticks exhibited less crying, less sleep disruption, and fewer state changes after the heelstick than without tucking (Obeidat, Kahalaf, Callister, & Froelicher, 2009). Combining oral sucrose with sucking with or without tucking during heelsticks resulted in significantly more quiet sleep and less crying than in infants without any intervention (Liaw et al., 2013). Lan et al. (2018) found that when nurses used a supportive care bundle, sleep latency was lower than in preterm infants receiving standard care. Rocking was not effective in reducing cry and facial expressions in preterm infants in response to a heelstick, although the infants were in quiet sleep more (Johnston et al., 1997). Thus, there is evidence that use of swaddling and pacifiers with sucrose can help reduce the sleeping and waking changes caused by painful procedures. However, additional research is needed to determine the effects of other comfort measures and how comfort measures affect more severe pain, such as postoperative pain.

Social Interaction. Sleeping and waking states are known to influence the interactions between full-term and premature infants and their mothers after term age, and in turn maternal interactions alter infant sleep–wake patterns. For example, infant crying may lead the mother to pick up the infant. At another time, a mother may awaken a sleeping infant for a feeding, thereby altering the infant's sleeping and waking patterns. Mothers have been found to exhibit different patterns of interactions when infants are in different states (Rosenthal, 1983). In addition, maternal emotional stress has been found to relate to the amount of night sleeping that full-term infants exhibit at 4 and 12 months (Becker, Chang, et al., 1991).

Social interaction is known to affect sleep–wake patterns of premature infants after hospital discharge, and sleep–wake patterns in turn alter social interactions. At 4 to 6 weeks corrected age, breastfed premature infants exhibited more crying, especially during daytime, than formula-fed infants did (Thomas, 2000). At 6 months corrected age, premature infants were more likely to be drowsy or asleep during feeding and alert during nonfeeding periods, and the behaviors of mothers differed during feeding and nonfeeding (Holditch-Davis et al., 2000). Mothers were more likely to engage in behaviors that involved close contact during feeding, such as holding, having body contact, and rocking their infants, whereas during nonfeeding periods, they were more likely to engage in more distal behaviors, such as gesturing and playing with the infant. Mothers who displayed more sensitive interactions or less negative affect had infants who took more naps and slept more in the daytime (Schwichtenberg, Anders, Vollbrecht, & Poehlmann, 2011; Schwichtenberg & Poehlmann, 2009; Schwichtenberg, Shah, & Poehlmann, 2013). Conversely, preterm infants with higher sleep cyclicity scores at term were

found to experience greater synchrony with their mothers at 3 months corrected age (Feldman, 2006).

Less is known about the effect of social interaction in the hospital on infant sleeping and waking states. Minde, Whitelaw, Brown, and Fitzhardinge (1983) found that ill preterm infants exhibited less eye opening—and thus probably less waking—when they were interacting with their mothers than did healthier preterm infants. Mothers report being aware of the sleeping and waking behaviors of their preterm infants—especially eye movements, orientation, and body movements—when they attempt to interact; they also report having used specific infant responses as guides to increase or decrease their interactive activity (Oehler, Hannan, & Catlett, 1993). Waking, eye opening, increased body movements, positive facial expressions, and calming encouraged increased interaction; body movements, negative facial expressions, and withdrawing discouraged maternal interaction. However, preterm infants exhibited the positive interactive behaviors for rather small portions of the time with their mothers (Oehler, 1995).

Moreover, social stimulation affects the physiologic status of preterm infants. The variation in infant oxygen saturation during parent touching was related to behavioral state and GA, such that infants who were more aroused and awake at the beginning of touch and had younger GAs at birth showed greater variation in their oxygen saturations (Harrison, Leeper, & Yoon, 1991). Using a standardized protocol of social stimulation, Eckerman, Oehler, Medvin, and Hannan (1994) found that preterm infants of at least 33 weeks' postmenstrual age responded to talking by eye opening and arousal, but when touching was added to the talking, the infants showed increased periods of closed eyes and negative facial expressions. Infants with more neurologic insults showed even greater negative responses to touching. This finding suggests that preterm infants are responsive to social stimulation of low intensity, but if the intensity of social stimulation is increased, they are no longer able to cope with it. Medical complications further decrease infants' ability to cope with moderate-intensity social stimulation.

Preterm infants have also been found to respond differently to nurses and parents. In one study, preterm infants opened their eyes more when interacting with parents than when interacting with nurses (Minde, Ford, Celhoffer, & Boukydis, 1975). In another study with sicker infants, preterm infants spent more time in active sleep and less time in sleep–wake transition when with their parents than when with nurses (Miller & Holditch-Davis, 1992). In both of these studies, parents and nurses behaved differently toward infants, with nurses more likely to engage in routine nursing and medical procedures and parents more likely to hold infants and provide positive social stimulation. These findings suggest that preterm infants respond to the less active, more social stimulation provided by parents at first by sleeping and then, as they mature, by awakening to engage in interaction. The early sleeping may serve to conserve infant energy consumption and promote growth.

Kangaroo care, mothers holding their preterm infants in skin-to-skin contact, has been found, in many studies, to increase the amount of sleeping—especially quiet sleep—and decrease crying and sleep–wake transition as compared with periods when the infant is alone in the incubator (Chwo et al., 2002; Lorenz et al., 2017, Ludington-Hoe et al., 2006; Scher et al., 2009), or when infants are being held in the mothers' arms (Bastani, Rajai, Farsi, & Als, 2017). In addition, preterm infants experiencing kangaroo care show more mature EEG patterns than infants not experiencing kangaroo care (Kaffashi, Scher, Ludington-Hoe, & Loparo, 2013). A few researchers, however, have not found any changes in state patterns during kangaroo care (de Leeuw, Colin, Dunnebier, & Mirmiran, 1991). Studies using historical controls or allowing mothers to choose whether they wanted to provide kangaroo care found that infants receiving kangaroo care had more rapid maturation of sleep–wake states (longer bouts of quiet sleep and alertness and shorter bouts of active sleep) and higher orientation and state scores on the NBAS (Feldman & Eidelman, 2003; Ohgi et al., 2002), and that by 10 years of age, the children had better organized sleep than children not receiving kangaroo care (Feldman, Rosenthal, & Eidelman, 2014).

Finally, interventions to promote emotional connections between mothers and their preterm infants have had effects on infant sleeping and waking. Infants receiving the Family Nurture Intervention (kangaroo care combined with stress reduction for the mothers) during the preterm period showed increases in EEG power in the frontal area during both active and quiet sleep at term (Welch et al., 2014) and faster development of cortical patterns within sleep (Welch et al., 2017).

Infant Stimulation. A number of the stimulation interventions used with preterm infants are known to affect sleeping and waking states. In some cases, the goal of the intervention is to alter sleeping and waking states either to lower the infant's arousal so as to provide more energy for growth or to promote more mature state patterns. In other cases, the state effects are side effects of interventions that were designed to alter other aspects of the infant's functioning. This section examines the effects of several different types of infant stimulation interventions currently in use in NICUs.

Nonnutritive sucking is an intervention that has been variously used to soothe irritable infants and to promote feedings and growth. It is known to decrease restlessness and increase sleep time, particularly quiet sleep, in full-term and preterm infants (Liaw et al., 2012; Schwartz, Moody, Yarandi, & Anderson, 1987). Nonnutritive sucking is effective in reducing crying after painful procedures and promoting either alertness or sleeping (Fearon et al., 1997). When given to preterm infants just before feedings, nonnutritive sucking helps them to arouse into a quiet, waking state and then maintain this state, in which they are most likely to feed effectively (Kamhawy, Holditch-Davis, Alsharkawy, Alrafay, & Corazzini, 2014; Pickler, Frankel, Walsh, & Thompson, 1996). When nonnutritive sucking was used as an intervention to bring preterm infants to a waking state before feeding, infants receiving the intervention took five fewer days to achieve full oral feedings than control group infants (McCain, Gartside, Greenberg, & Lott, 2001). Other researchers did not find a change of state with nonnutritive sucking but did find that preterm infants who received nonnutritive sucking before feedings had higher feeding performance scores and more sleep after feedings (Pickler, Higgins, & Crummette, 1993).

Swaddling has been used to modify preterm infant sleep–wake states. Clothing that provided swaddling for preterm infants was associated with more quiet sleep (Kitase et al., 2017). Combined swaddling and nesting have been found to increase quiet sleep and total sleep time as compared to periods when the infants were not receiving any intervention (Abdeyazdan, Mohammadian-Ghahfarokhi, Ghazavi, & Mohammadizadeh, 2016).

Gentle touching is another form of infant stimulation. Harrison, Oliveet, Cunningham, Bodin, and Hicks (1996) provided 15 minutes of daily gentle human touch to preterm infants in the first 2 weeks of life. Infants had significantly less active sleep and motor activity during the periods of gentle touching. When the frequency of this intervention was increased to three times a day, preterm infants exhibited less active sleep, motor activity, and distress during gentle touching periods but did not differ from control group infants on any outcome variable (Harrison, Williams, Berbaum, Stem, & Leeper, 2000). After gentle touching and after

Yakson touch, a Korean process of gentle caresses, preterm infants exhibited greater sleep and less waking and fussing than infants in a control group (Bahman Bijari, Iranmanesh, Eshghi, & Baneshi, 2012; Im & Kim, 2009), and one study found that this effect was stronger for infants receiving Yakson touch (Im, Kim, & Cain, 2009).

Infant massage is another common infant stimulation technique. It provides both tactile and kinesthetic stimulation, because it is necessary to move the infant to provide tactile stimulation to different parts of the body. The purpose of this type of stimulation is primarily to promote growth and augment development, but it also affects infant sleeping and waking states. White-Traut and Pate (1987) used the Rice Infant Sensomotor Stimulation, a 10-minute structured massage of the infant's entire body from head to toe, to provide extra stimulation for growing preterm infants. They found that during massage infants were more alert. In another study, the intervention protocol was altered to be more contingent to infant cues (White-Traut, Nelson, Silvestri, Patel, & Kilgallon, 1993). Again, the experimental infants showed increased alertness during the intervention and continued to be alert for 30 minutes afterward. In another study, the massage intervention was compared with auditory stimulation alone; auditory stimulation along with massage; and auditory, massage, and rocking combined (White-Traut, Nelson, Silvestri, Cunningham, & Patel, 1997). Infants showed increasing alertness during the intervention in the massage and massage plus auditory groups, whereas the auditory group showed more quiet sleep. The massage, auditory, and rocking group showed minimal changes during the intervention but sustained alertness for 30 minutes afterward. The combined auditory, massage, and rocking intervention was then tested on preterm infants with periventricular leukomalacia (White-Traut et al., 1999). Infants who received this combined intervention showed an increase in alertness over the intervention period and were hospitalized for nine fewer days. Increased alertness also resulted from this intervention when it was used with infants with prenatal substance exposure (White-Traut et al., 2002). A similar massage protocol that involved both tactile and kinesthetic stimulation resulted in preterm infants showing more mature electrical activity on the EEG (Guzzetta et al., 2011).

In other studies, stroking of the infant's body followed by passive flexion and extension of the extremities for 15 minutes three times a day for 5 to 10 days was shown to result in increased weight gain in preterm infants (Dieter, Field, Hernandez-Reif, Emory, & Redzepi, 2003; Scafidi et al., 1990), possibly because of increased vagal activity, gastric motility, and IGF-1 (Field, Diego, & Hernandez-Reif, 2011). During massage treatments, infants exhibited more active sleep (Scafidi et al., 1990), but whether these state effects persisted after the treatment period is less clear. In two studies, massage-treated infants exhibited better scores on the NBAS and spent less time asleep (Dieter et al., 2003), whereas in another, no differences in the state organization of treated and control infants were found (Scafidi et al., 1990). Infants receiving moderate pressure massage showed a greater decrease in active sleep, less agitated behavior, and less crying than infants receiving a light pressure massage (Field et al., 2004; Field, Diego, Hernandez-Reif, Deeds, & Figuereido, 2006).

Rocking is a form of infant stimulation usually performed in order to soothe the infant. It has been administered either directly while holding the infant or by placing the infant in special cribs or incubators modified to rock at specific speeds. The immediate effects of rocking are reduced crying (Byrne & Horowitz, 1981). However, the rhythm and direction of rocking are important in determining which of the other states the infant was most likely to exhibit (Byrne & Horowitz, 1981). Exposing preterm infants to rocking over a 2-week period had longer lasting results (Cordero, Clark, & Schott, 1986). They exhibited increased quiet sleep and decreased active sleep.

In yet another study, preterm infants were placed in a nonrigid reclining chair twice a day for 3 hours from about 30 weeks' postmenstrual age until hospital discharge (Provasi & Lequien, 1993). Sleeping and waking states were observed for a 2-hour period for control infants and two 2-hour periods for the experimental infants (once in their beds and once in an infant seat) shortly before discharge. Experimental infants spent more time in quiet sleep and active sleep and less time in quiet and agitated waking than the control group infants, but no differences were found in the state patterns of the experimental infants when in their bed and in the infant seat.

Music has also been used as a form of infant stimulation in the NICU. Amon et al. (2006) found that preterm infants experiencing live music as compared to recorded music or no music showed a greater reduction in HR and more sleep 30 minutes after the intervention. Six hours of music for late preterm infants resulted in fewer interruptions in quiet sleep and more mature sleep cycles compared to standard care periods (Stokes, Agthe, & El Metwally, 2018). Loewy, Stewart, Dassler, Telsey, and Homel (2013) compared three different types of music to routine NICU sounds. Infants receiving any of the music interventions had more active sleep than during the control period, but only after listening to the lullaby did infants show less activity during quiet alert. Dorn et al. (2014). compared the effects of a lullaby with maternal voice recording presented daily for 30 minutes for 2 weeks. These interventions did not differ in their effects on sleep–wake behaviors or activity cycles.

In a final type of infant stimulation, Thoman and Graham (1986) placed a "breathing" stuffed bear in the incubator with a preterm infant. The goal of this intervention was to provide a form of rhythmic stimulation that would help the infant organize his or her sleeping and waking patterns. In addition, this form of stimulation was voluntary. Because the bear took up only a small part of the incubator and babies were usually put to sleep in positions in which they were not in physical contact with the bear, infants could choose whether or not to remain in contact with the bear whenever their random movements brought them into contact with it. As compared with the control group, experimental infants spent a much greater percentage of time in contact with the area of the incubator with the bear. By the end of the intervention period, experimental infants exhibited significantly more quiet sleep time. This study has been replicated with two additional samples, and both have shown increased contact with the breathing bear as well as more quiet sleep and less active sleep than infants given a nonbreathing bear (Ingersoll & Thoman, 1994; Thoman, Ingersoll, & Acebo, 1991).

Usefulness of Neonatal Sleep–Wake States for Assessment. Sleeping and waking states are ubiquitous characteristics of neonates. The infant's behavioral and physiologic responses are filtered through neural controls mediated by the sleeping and waking states. Although it is certainly possible to give competent nursing care to high-risk infants without considering their sleep–wake states, recognizing specific states will enable the nurse to better interpret both physiologic and behavioral changes. By observing sleeping and waking, the nurse will be able to determine whether physiologic parameters are consistent with those expected in a particular state. Changes in sleeping and waking patterns can be used to help the nurse identify the need for interventions and to aid the evaluation of these interventions. Most importantly, by observing sleeping and waking behaviors, the nurse will come to know each infant better and thus be better

able to provide individualized care. This knowledge of individual infants can then be shared with parents to help them develop positive interactions with their children.

SUMMARY

High-risk infants are both dependent on and vulnerable to their early environment—the NICU and intermediate nursery—to maintain their physiologic function, to promote growth and development, and to provide opportunities for the organization of state, behavioral, and social responsiveness. The immaturity and physiologic and neurobehavioral instability of these infants make them particularly vulnerable to environments that do not support their emerging organization and patterns or that do not attend to their cues and respond appropriately. Nurses can and do play a big role in controlling sleep in the NICU environment. It is important that parents are included in these efforts to promote positive sleep–wake patterns in the NICU and once the infant is home.

In summary, the goals in addressing the neurobehavioral needs of high-risk infants are the following:

1. Provide an environment that enhances and supports the infant's developing capabilities and sleep–wake patterns
2. Protect the infant from sensory overload and minimize stressors
3. Assist parents in understanding their infant's unique abilities including sleep–wake patterns
4. Help parents interact with their infant in ways appropriate to the infant's health status, sleep–wake state, and level of maturity

No matter how vigilantly we care for babies in the NICU, it is important to recognize that every interaction and touch provided to a preterm infant affects brain development and contributes to the overall developmental outcome of the infant, and impacts the family. There is ample evidence that neuroprotective family-centered developmental care in the NICU results in improved neonatal and neurodevelopmental outcomes, increased family satisfaction, and even enhanced employee satisfaction once a culture of change has been established. Both the risk of initial brain injury and subsequent neurodevelopmental problems can be reduced by optimizing currently approved and recommended best neuroprotective practices (Altimier & Phillips, 2013, 2016; Altimier & White, 2014). By consistently applying the principles and practices we know to be beneficial for extremely premature infants, we can improve the NICU experience for babies, families, and staff and make a significant difference in the long-term physical, cognitive, and emotional health and well-being of these fragile babies and their families.

Consistent acceptance, practice, and accountability to neuroprotective family-centered developmentally supportive care standards must be established to provide high-quality care for infants and families. Use of established guidelines, policies, and procedures to guide neonatal practice is essential. To provide this level of care and optimize the experience of neonates in the NICU environment, an understanding of their behavioral capabilities, their surrounding physical environment, and their family support system is essential. Healthcare professionals need to be cognizant of the growing body of research regarding the impact of the NICU environment and family participation on neurodevelopmental outcomes. Changes in developmental care can often begin with a few caregivers altering the way they care for premature infants and their families. Role modeling, mentoring, coaching, and collaboration are essential in the promotion of optimal neuroprotective family-centered developmentally supportive care.

PARENT VOICES

Jenny R. McCormick

My son was only 2 days old when the doctor came into my recovery room to let me know that his brain had hemorrhaged–intraventricular hemorrhage (IVH). I was told that the hemorrhage was on the left side of his brain. As the days progressed, my son's brain bleed went from a grade I bleed to a bilateral grade III/IV bleed. This was by far the scariest time for me during our NICU journey. We became very familiar with waiting for results from ultrasounds and meeting with his neurologist. Because of his brain bleed, we were given such a poor prognosis and our fears were many. Thankfully, we had a great NICU team working with us to keep us informed, to provide education in a clear manner that made it easier for us to understand what we were dealing with; above all, as they seemed to understand my worry and exhaustion, they went out of their way to provide updates daily and as soon as possible. This, in turn, helped my husband and me learn how to advocate for our child, research, and ask questions, while feeling like our voices were being heard. Today, my son is 6 years old and, though delayed in many areas, he is thriving.

Keira Sorrells

Aside from having the most wonderfully supportive lactation nurses in our unit, the neonatal therapists were equally incredible. I will never forget when I walked in for a visit and our primary nurse said she had scheduled an appointment for the occupational therapist (OT) to teach me infant massage. This was a highlight of our time in the NICU where the OT gently coached me and encouraged me to care for my daughter using the healing power of touch. She taught me important cues to look for as well as potential areas for concern as we worked together. Being able to provide this type of massage for my girls allowed me an additional manner in which to bond, empowered me to feel more like a "real" mom, and was something I continued to do for my girls into their toddler years.

ONLINE RESOURCES

Lester, B. M., Andreozzi-Fontaine, L., Tronick, E., & Bigsby, R. (n.d.). Assessment and evaluation of the high risk neonatal: The NICU network neurobehavioral scale. *Journal of Visualized Experiments*, (90), e3368. doi:10.3791/3368

Stanford Children's Health | Lucile Packard Children's Hospital Stanford. (2014). *Neurodevelopment of preterm babies* [Video file]. Retrieved from https://www.youtube.com/watch?v=T7DdUq8Gyf4

UCSF NICU-Neonatal Neurodevelopmental Care. Retrieved from https://www.youtube.com/watch?v=fJFvl1AgDYw

KEY REFERENCES

Aarnoudse-Moens, C. S. H., Weisglas-Kuperus, N., van Goudoever, J. B., & Oosterlaan, J. (2009). Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children. *Pediatrics 124*(2), 717–728. doi:10.1542/peds.2008-2816

Abdeyazdan, Z., Mohammadian-Ghahfarokhi, M., Ghazavi, Z., & Mohammadizadeh, M. (2016). Effects of nesting and swaddling on the sleep duration of premature infants hospitalized in neonatal intensive care units. *Iranian Journal of Nursing and Midwifery Research, 21*(5), 552–556. doi:10.4103/1735-9066.193422

Acebo, C., & Thoman, E. B. (1995). Role of infant crying in the early mother–infant dialogue. *Physiology and Behavior, 57*(3), 541–547. doi:10.1016/0031-9384(94)00345-6

Adam, K., & Oswald, I. (1984). Sleep helps healing. *British Medical Journal, 289*(6456), 1400–1401. doi:10.1136/bmj.289.6456.1400

Adam-Darque, A., Grouiller, F., Vasung, L., Ha-Vinh Leuchter, R., Pollien, P., Lazeyras, F., Huppi, P. S. (2018). fMRI-based neuronal response to new odorants in the newborn brain. *Cerebral Cortex, 28*(8), 2901–2907. doi:10.1093/cercor/bhx167

Adams-Chapman, I., Heyne, R., DeMauro, S., Duncan, A., Hintz, S., Pappas, A., . . . Higgins, R. D. (2018). Neurodevelopmental impairment among extremely preterm infants in the neonatal research network. *Pediatrics, 141*(5), e20173091. doi:10.1542/peds.2017-3091

Agrawal, S., Rao, S., Bulsara, M., & Patole, S. (2018). Prevalence of autism spectrum disorder in preterm infants: A meta-analysis. *Pediatrics, 142*(3), e20180134. doi:10.1542/peds.2018-0134

Allotey, J., Zamora, J., Cheong-See, F., Kaldindi, M., Arroyo-Manzano, D., Asztalos, E., . . . Thangaratinam, S. (2018). Cognitive, motor, behavioural and academic performances of children born preterm: A meta-analysis and systematic review involving 64061 children. *BJOG: An International Journal of Obstetrics & Gynaecology, 125*(1), 16–25. doi:10.1111/1471-0528.14832

Als, H. (1982). Toward a synactive theory of development: Promise for the assessment and support of infant individuality. *Journal of Infant Mental Health, 3*(4), 229–243. doi:10.1002/1097-0355(198224)3:4%3C229::AID-IMHJ2280030405%3E3.0.CO;2-H

Als, H. (1986). A synactive model of neonatal behavioral organization: Framework for assessment of neurobehavioral development in the premature infant and for support of infants and parents in the neonatal intensive care environment. Part 1: Theoretical framework. *Physical and Occupational Therapy in Pediatrics, 6*(3/4), 3–53. doi:10.1080/J006v06n03_02

Als, H., Butler, S., Kosta, S., & McAnulty, G. (2005). The assessment of preterm infants' behavior (APIB): Furthering the understanding and measurement of neurodevelopmental competence in preterm and full-term infants. *Mental Retardation & Developmental Disabilities Research Reviews, 11*(1), 94–102. doi:10.1002/mrdd.20053

Als, H., Duffy, F. H., & McAnulty, G. B. (1988). Behavioral differences between preterm and fullterm newborns as measured on the APIB System scores. *Infant Behavior and Development*, *11*(3), 305–318. doi:10.1016/0163-6383(88)90016-1

Als, H., Lawhon, G., Brown, E., Gibes, R., Duffy, F. H., McAnulty, G., & Blickman, J. G. (1986). Individualized behavioral and environmental care for the very-low-birth-weight preterm infant at high risk for bronchopulmonary dysplasia: Neonatal intensive care unit and developmental outcome. *Pediatrics, 78*(6), 1123–1132. Retrieved from https://pediatrics.aappublications.org/content/78/6/1123.full

Als, H., Lawhon, G., Duffy, F. H., McAnulty, G. B., Gibes-Grossman, R., &. Blickman, J. G. (1994). Individualized developmental care for the very-low-birth-weight preterm infant: Medical and neurofunctional effects. *Journal of the American Medical Association, 272*(11), 853–858. doi:10.1001/jama.1994.03520110033025

Als, H., Lester, B. M., Tronick, E. C., & Brazelton, T. B. (1982). Manual for the assessment of preterm infant behavior (APIB). In H. E. Fitzgerald & M. Yogman (Eds.), *Theory and research in behavioral pediatrics* (Vol. 1, pp. 64–133). New York, NY: Plenum Press.

Altimier, L. (2015, September). Neuroprotective core measure 1: The healing NICU environment. *Newborn and Infant Nursing Reviews, 15*(3), 89–94. doi:10.1053/j.nainr.2015.06.014

Altimier, L., & Phillips, R. M. (2013). The neonatal integrative developmental care model: Seven neuroprotective core measures for family-centered developmental care. *Newborn and Infant Nursing Reviews, 13*(1), 9–22. doi:10.1053/j.nainr.2012.12.002

Altimier, L., & Phillips, R. M. (2018). Neuroprotective care of extremely preterm infants in the first 72 hours after birth. *Critical Care Nursing Clinics of North America, 30*(4), 563–583. doi:10.1016/j.cnc.2018.07.010

Altimier, L., & White, R. (2014). The neonatal intensive care unit (NICU) environment. In C. Kenner & J. Lott (Eds.), *Comprehensive neonatal nursing care* (5th ed., pp. 722–738). New York, NY: Springer Publishing Company.

American Academy of Pediatrics Task Force on Sudden Infant Death Syndrome. (2011, November). SIDS and other sleep-related infant deaths: Expansion of recommendations for a safe infant sleeping environment. *Pediatrics, 128*(5), e1341–e1367. doi:10.1542/peds.2011-2285

Amiel-Tison, C. (1976). A method for neurologic evaluation within the first year of life. *Current Problems in Pediatrics, 7*(1), 3–50. doi:10.1016/S0045-9380(76)80006-0

Amon, S., Shapsa, A., Forman, L., Regev, R., Bauer, S., Litmanovitz, I., & Dolfin, T. (2006). Live music is beneficial to preterm infants in the neonatal intensive care unit environment. *Birth, 33*(2), 131–136. doi:10.1111/j.0730-7659.2006.00090.x

Anders, T., Emde, R., & Parmelee, A. (Eds.). (1971). *A manual of standardized terminology, techniques and criteria for scoring of states of sleep and wakefulness in newborn infants*. Los Angeles, CA: UCLA Brain Information Service/BRI Publications Office.

Anderson, G. C. (1999). Kangaroo care of the premature infant. In E. Goldson (Ed.), *Nurturing the premature infant: Developmental interventions in the neonatal intensive care nursery* (pp. 131–160). New York, NY: Oxford University Press.

Anderson, J. G., Baer, R. J., Partridge, J. C., Kuppermann, M., Franck, L. S., Rand, L., . . . Rogers, E. E. (2016). Survival and major morbidity of extremely preterm infants: A population-based study. *Pediatrics, 138*(1), e20154434. doi:10.1542/peds.2015-4434

Anderson, P. J. (2014). Neuropsychological outcomes of children born very preterm. *Seminars in Fetal & Neonatal Medicine, 19*(2), 90–96. doi:10.1016/j.siny.2013.11.012

Anderson, P. J. (2018). Cognitive outcomes in children born very preterm are not improving. *Acta Paediatrica, 107*(11), 1846–1847. doi:10.1111/apa.14544

Apkarian, P., Mirmiran, M., & Tijssen, R. (1991). Effects of behavioural state on visual processing in neonates. *Neuropediatrics, 22*(2), 85–91. doi:10.1055/s-2008-1071422

Appler, J. M., & Goodrich, L. V. (2011). Connecting the ear to the brain: Molecular mechanisms of auditory circuit assembly. *Progress in Neurobiology, 93*(4), 488–508. doi:10.1016/j.pneurobio.2011.01.004

Arditi-Babchuk, H., Feldman, R., & Eidelman, A. I. (2009). Rapid eye movement (REM) in premature neonates and developmental outcome at 6 months. *Infant Behavior and Development, 32*(1), 27–32. doi:10.1016/j.infbeh.2008.09.001

Ariagno, R. L., Mirmiran, M., Adams, M. M., Saporito, A. G., Dubin, A. M., & Baldwin, R. B. (2003). Effect of position on sleep, heart rate variability, and QT interval in preterm infants at 1 and 3

months' corrected age. *Pediatrics*, *111*(3), 622–625. doi:10.1542/peds.111.3.622

Ariagno, R. L., van Liempt, S., & Mirmiran, M. (2006). Fewer spontaneous arousals during prone sleep in preterm infants at 1 and 3 months corrected age. *Journal of Perinatology, 26*(5), 306–312. doi:10.1038/sj.jp.7211490

Armitage, R., Flynn, H., Hoffmann, R., Vazquez, D., Lopez, J., & Marcus, S. (2009). Early developmental changes in sleep in infants: The impact of maternal depression. *Sleep, 32*(5), 693–696. doi:10.1093/sleep/32.5.693

Asaka, Y., & Takada, S. (2010). Activity-based assessment of the sleep behaviors of VLBW preterm infants and full-term infants at around 12 months of age. *Brain and Development, 32*(2), 150–155. doi:10.1016/j.braindev.2008.12.006

Axelin, A., Cilio, M. R., Asunis, M., Peloquin, S., & Franck, L. S. (2013). Sleep-wake cycling in a neonate admitted to the NICU: A video-EEG case study during hypothermia treatment. *Journal of Perinatal and Neonatal Nursing, 27*(3), 263–273. doi:10.1097/JPN.0b013e31829dc2d3

Axelin, A., Kirjavainen, J., Salanterä, S., & Lehtonen, L. (2010). Effects of pain management on sleep in preterm infants. *European Journal of Pain, 14*(7), 752–758. doi:10.1016/j.ejpain.2009.11.007

Bahman Bijari, B., Iranmanesh, S., Eshghi, F., & Baneshi, M. R. (2012). Gentle human touch and Yakson: The effect on preterm's behavioral reactions. *International Scholarly Research Network Nursing, 2012*, 750363. doi:10.5402/2012/750363

Barbeau, D. Y., & Weiss, M. D. (2017). Sleep disturbances in newborns. *Children, 4*(10), E90. doi:10.3390/children4100090

Barbosa, V., & Powlesland, J. (2018). Behavioral organization in infants with intraventricular hemorrhage: Characteristics and clinical implications. *Neonatal Network, 37*(5), 310–318. doi:10.1891/0730-0832.37.5.310

Barnard, K. E., & Blackburn, S. (1985). Making a case for studying the ecological niche of the newborn. *NAACOG Invitational Research Conference. Birth defects: Original Article Series, 21*(3), 71–88.

Bastani, F., Rajai, N., Farsi, Z., & Als, H. (2017). The effects of kangaroo care on the sleep and wake states of preterm infants. *Journal of Nursing Research, 25*(3), 231–239. doi:10.1097/JNR.0000000000000194

Bauer, C. R., Langer, J. C., Shankaran, S., Bada, H. S., Lester, B., Wright, L. L., . . . Verter, J. (2005). Acute neonatal effects of cocaine exposure during pregnancy. *Archives of Pediatric and Adolescent Medicine, 159*(9), 824–834. doi:10.1001/archpedi.159.9.824

Bayley, N. (1993). *Bayley scales of infant development* (2nd ed.). San Antonio, TX: The Psychological Corporation.

Bayley, N. (2005). *Bayley scales of infant and todler development* (3rd ed.). Upper Saddle River, NJ: Pearson.

Becker, P. T., Chang, A., Kameshima, S., & Bloch, M. (1991). Correlates of diurnal sleep patterns in infants of adolescent and adult single mothers. *Research in Nursing and Health, 14*(2), 97–108. doi:10.1002/nur.4770140204

Becker, P. T., Grunwald, P. C., Moorman, J., & Stuhr, S. (1991). Outcomes of developmentally supportive nursing care for very low birth weight infants. *Nursing Research, 40*(3), 150–155. doi:10.1097/00006199-199105000-00006

Becker, P. T., Grunwald, P. C., Moorman, J., & Stuhr, S. (1993). Effects of developmental care on behavioral organization in very-low-birth-weight infants. *Nursing Research, 42*(4), 214–220. doi:10.1097/00006199-199307000-00005

Becker, P. T., & Thoman, E. B. (1982). Waking activity: The neglected state of infancy. *Brain Research, 256*(4), 395–400. doi:10.1016/0165-3806(82)90182-1

Beker, F., Opie, G., Noble, E., Jiang, Y., & Bloomfield, F. H. (2017). Smell and taste to improve nutrition in very preterm infants: A randomized controlled pilot trial. *Neonatology, 111*(3), 260–266. doi:10.1159/000450883

Bennett, A. J., Hopkins, W. D., Feldman, T., Gazzola, V., Giedd, J., Lamb, M.E., . . . Tottenham, N. (2017). Neural foundations of variability in attachment. In H. Keller & K. A. Bard (Eds.), *The cultural nature of attachment and contextualizing relationships and development*. Cambridge, MA: MIT Press.

Bergman, N. J. (2014). The neuroscience of birth–and the case for zero separation. Curationis, 37(2), 1–4. doi:10.4102/curationis.v37i2.1440

Bergman, N. J. (2015). Neuroprotective core measures 1-7: Neuroprotection of skin-to-skin contact (SSC). *Newborn and Infant Nursing Reviews, 15*(3), 142–146. doi:10.1053/ j.nainr.2015.06.006

Bernert, G., von Siebenthal, K., Seidl, R., Vanhole, C., Devlieger, H., & Casaer, P. (1997). The effect of behavioural states on cerebral oxygenation during endotracheal suctioning of preterm babies. *Neuropediatrics, 28*(2), 111–115. doi:10.1055/s-2007-973682

Bertelle, V., Mabin, D., Adrien, J., & Sizun, J. (2005). Sleep of preterm neonates under developmental care or regular environmental conditions. *Early Human Development, 81*(7), 595–600. doi:10.1016/j.earlhumdev.2005.01.008

Bhat, R. Y., Hannam, S., Pressler, R., Rafferty, G. F., Peacock, J. L., & Greenough, A. (2006). Effect of prone and supine position on sleep, apneas, and arousal in preterm infants. *Pediatrics, 118*(1), 101–107. doi:10.1542/peds.2005-1873

Black, B., Holditch-Davis, D., Schwartz, T., & Scher, M. S. (2006). Effects of antenatal magnesium sulfate and corticosteroid therapy on sleep states of preterm infants. *Research in Nursing and Health*, *29*(4), 269–280. doi:10.1002/nur.20141

Blackburn, S. (2018). *Maternal, fetal and neonatal physiology: A clinical perspective* (5th ed.). St. Louis, MO: Elsevier.

Blackburn, S., & Barnard, K. E. (1985). Analysis of caregiving events in preterm infants in the special care unit. In A. Gottfried & J. Gaiter (Eds.), *Infants under stress: Environmental neonatology* (pp. 113–129). Baltimore, MD: University Park Press.

Blackburn, S., & Patteson, D. (1991). Effects of cycled lighting on activity state and cardiorespiratory function in preterm infants. *Journal of Perinatal and Neonatal Nursing, 4*(4), 47–54. doi:10.1097/00005237-199103000-00009

Blencowe, H., Lee, A. C., Cousens, S., Bahalim, A., Narwal, R., Zhong, N., . . . Lawn, J. E. (2013). Preterm birth-associated neurodevelopmental impairment estimates at regional and global levels for 2010. *Pediatric Research, 74*(Suppl. 1), 17–34. doi:10.1038/pr.2013.204

Bloomfield, F., Alexander, T., Muelbert, M., & Beker, F. (2017). Smell and taste in the preterm infant. *Early Human Development, 114*, 31–34. doi:10.1016/j.earlhumdev.2017.09.012

Borghese, I. F., Minard, K. L., & Thoman, E. B. (1995). Sleep rhythmicity in premature infants: Implications for developmental status. *Sleep, 18*(7), 523–530. doi:10.1093/sleep/18.7.523

Borsani, E., Della Vedova, A., Rezzani, R., Rodella, L., & Cristini, C. (2018). Correlation between human nervous system development and acquisition of fetal skills: An overview. *Brain & Development, 41*(3), 225–233. doi:10.1016/j.braindev.2018.10.009

Bouyssi-Kobar, M., Brossard-Racine, M., Jacobs, M., Murnick, J., Chang, T., & Limperopoulos, C. (2018). Regional microstructural organization of the cerebral cortex is affected by preterm birth. *NeuroImage: Clinical, 18*, 871–880. doi:10.1016/j.nicl.2018.03.020

Brandon, D. H., & Holditch-Davis, D. (2005). Validation of an instrumented sleep-wake state assessment against biobehavioral assessment. *Newborn and Infant Nursing Reviews, 5*(3), 109–115. doi:10.1053/j.nainr.2005.04.002

Brandon, D. H., Holditch-Davis, D., & Belyea, M. (1999). Nursing care and the development of sleeping and waking behaviors in preterm infants. *Research in Nursing and Health, 22*, 217–229. doi:10.1002/(SICI)1098-240X(199906)22:3%3C217::AID-NUR4%3E3.0.CO;2-U

Brandon, D. H., Holditch-Davis, D., & Belyea, M. (2002). Preterm infants born at less than 31 weeks' gestation have improved growth in cycled light compared with continuous near darkness. *Journal of Pediatrics, 140*(2), 192–199. doi:10.1067/mpd.2002.121932

Brandon, D. H., Holditch-Davis, D., & Winchester, D. M. (2005). Factors affecting early neurobehavioral and sleep outcomes in preterm infants. *Infant Behavior and Development, 28*(2), 206–219. doi:10.1016/j.infbeh.2005.02.005

Brandon, D. H., Silva, S. G., Park, J., Malcolm, W., Kamhawy, H., & Holditch-Davis, D. (2017). Timing for the introduction of cycled light for extremely preterm infants: A randomized control trial. Research in Nursing and Health, 40(4), 294–310. doi:10.1002/nur.21797

Brazelton, T. B. (1984). *Neonatal behavioral assessment scale* (2nd ed.). Cambridge, MA: Cambridge University Press.

Brazelton, T. B., & Nugent, J. K. (1995). *Neonatal behavioral assessment scale*. London, England: MacKeith Press. Retrieved from https://www.perinatal.com.br/9SimposioIntNeoRJ/pdf/Aula08BrazeltonHutchon.pdf

Brazelton, T. B., & Nugent, J. (2011). *Neonatal behavioral assessment scale* (4th ed.). London, England: Mac Keith Press.

Brazy, J. E. (1988). Effect of crying on cerebral volume and cytochrome aa_3. *Journal of Pediatrics*, *112*(3), 457–461. doi:10.1016/S0022-3476(88)80336-6

Brossard-Racine, M., du Plessis, A. J., & Limperopoulos, C. (2015). Developmental cerebellar cognitive affective syndrome in ex-preterm survivors following cerebellar injury. *Cerebellum, 14*(2), 151–164. doi:10.1007/s12311-014-0597-9

Buehler, D. M., Als, H., Duffy, F. H., McAnulty, G. B., & Liederman, J. (1995). Effectiveness of individualized developmental care for low-risk preterm infants: Behavioral and electrophysiological evidence. *Pediatrics, 96*, 923–932. Retrieved from https://pediatrics.aappublications.org/content/96/5/923

Burnett, A., Cheong, J., & Doyle, L. W. (2018). Biological and social influences on the neurodevelopmental outcomes of preterm infants. *Clinics in Perinatology, 45*(3), 485–500. doi:10.1016/j.clp.2018.05.005

Bushdid, C., Magnasco, M., Vosshall, L., & Keller, A. (2014). Humans can discriminate more than 1 trillion olfactory stimuli. *Science, 343*(6177), 1370–1372. doi:10.1126/science.1249168

Byrne, J. M., & Horowitz, F. D. (1981). Rocking as a soothing intervention: The influence of direction and type of movement. *Infant Behavior and Development, 4*(2), 207–218. doi:10.1016/S0163-6383(81)80024-0

Campbell, S. K. (2005). *The test of infant motor performance. Test User's Manual* (Vol. 2). Chicago, IL: Infant Motor Performance Scales.

Cao Van, H., Guinand, N., Damis, E., Mansbach, A., Poncet, A., Hummel, T., & Landis, B. (2018). Olfactory stimulation may promote oral feeding in immature newborn: A randomized controlled trial. *European Archives of Oto-Rhino-Laryngology, 275*(1), 125–129. doi:10.1007/s00405-017-4796-0

Caravale, B., Sette, S., Cannoni, E., Marano, A., Riolo, E., Devescovi, A., . . . Bruni, O. (2017). Sleep characteristics and temperament in preterm children at two years of age. *Journal of Clinical Sleep Medicine, 13*(9), 1081–1088. doi:10.5664/jcsm.6728

Carmichael, K., Burns, Y., Gray, P., & O'Callaghan, M. (1997). Neuromotor behavioural assessment of preterm infants at risk for impaired development. *Australian Journal of Physiotherapy, 43*(2), 101–107. doi:10.1016/S0004-9514(14)60404-9

Chorna, O., Solomon, J. E., Slaughter, J. C., Stark, A. R., & Maitre, N. L. (2014). Abnormal sensory reactivity in preterm infants during the first year correlates with adverse neurodevelopmental outcomes at 2 years of age. *Archives of Disease in Childhood. Fetal and Neonatal Edition, 99*(6), F475–F479. doi:10.1136/archdischild-2014-306486

Chwo, M.-J., Anderson, G. C., Good, M., Dowling, D. A., Shia, S.-H., & Chu, D.-M. (2002). A randomized controlled trial of early kangaroo care for preterm infants: Effects on temperature, weight, behavior, and acuity. *Nursing Research, 10*(2), 129–142. doi:10.1097/01.JNR.0000347592.43768.46

Cohen, G., Xu, C., & Henderson-Smart, D. (1991). Ventilatory response of sleeping newborn to CO_2 during normoxic rebreathing. *Journal of Applied Physiology*, *71*(1), 168–174. doi:10.1152/jappl.1991.71.1.168

Collins, C. L., Barfield, C., Davis, P. G., & Horne, R. S. (2015). Randomized controlled trial to compare sleep and wake in preterm infants less than 32weeks of gestation receiving two different modes of non-invasive respiratory support. *Early Human Development, 91*(12), 701–704. doi:10.1016/j.earlhumdev.2015.09.011

Colombo, J., & Horowitz, F. D. (1987). Behavioral state as a lead variable in neonatal research. *Merrill-Palmer Quarterly*, *33*(4), 423–437.

Cordero, L., Clark, D. L., & Schott, L. (1986). Effects of vestibular stimulation on sleep states in premature infants. *American Journal of Perinatology, 3*(4), 319–324. doi:10.1055/s-2007-999888

Corff, K. E., Seidemanm, R., Venkataraman, P. S., Lutes, L., & Yates, B. (1995). Facilitated tucking: A non-pharmacologic comfort measure for pain in preterm neonates. *Journal of Obstetric, Gynecologic and Neonatal Nursing*, *24*, 143–147. doi:10.1111/j.1552-6909.1995.tb02456.x

Corwin, M. J., Lester, B. M., Sepkoski, C., Peuker, M., Kayne, H., & Golub, H. L. (1995). Newborn acoustic cry characteristics of infants subsequently dying of sudden infant death syndrome. *Pediatrics, 96*, 73–77. Retrieved from https://pediatrics.aappublications.org/content/96/1/73

Costeloe, K. L., Hennessy, E. M., Haider, S., Stacey, F., & Marlow, N. (2012). Short term outcomes after extreme preterm birth in England: Comparison of two birth cohorts in 1994 and 2006 (the EPICure studies). *British Medical Journal, 345*, 7976. doi:10.1136/bmj.e7976

Craciunoiu, O., & Holsti, L. (2017). A systematic review of the predictive validity of neurobehavioral assessments during the preterm period. *Physical & Occupational Therapy in Pediatrics, 37*(3), 292–307. doi:10.1080/01942638.2016.1185501

Cremer, M., Jost, K., Gensmer, A., Pramana, I., Delgado-Eckert, E., Frey, U., . . . Datta, A. N. (2016). Immediate effects of phototherapy on sleep in very preterm neonates: An observational study. *Journal of Sleep Research, 25*(5), 517–523. doi:10.1111/jsr.12408

Curzi-Dascalova, L. (1992). Physiological correlates of sleep development in premature and full-term neonates. *Neurophysiologie Clinique/Clinical Neurophysiology, 22*(2), 151–166. doi:10.1016/S0987-7053(05)80751-8

Curzi-Dascalova, L., Aujard, Y., Gaultier, C., & Rajguru, M. (2002). Sleep organization is unaffected by caffeine in premature infants. *Journal of Pediatrics, 140*(6), 766–771. doi:10.1067/mpd.2002.124383

Curzi-Dascalova, L., Bloch, J., Vecchierini, M., Bedu, A., & Vignolo, P. (2000). Physiological parameters evaluation following apnea in healthy premature infants. *Biology of the Neonate, 77*, 203–211. doi:10.1159/000014217

Curzi-Dascalova, L., Peirano, P., & Morel-Kahn, F. (1988). Development of sleep states in normal premature and fullterm newborns. *Developmental Psychobiology, 21*(5), 431–444. doi:10.1002/dev.420210503

Decima, P. F., Fyfe, K. L., Odoi, A., Wong, F. Y., & Horne, R. S. (2015). The longitudinal effects of persistent periodic breathing on cerebral oxygenation in preterm infants. *Sleep Medicine, 16*(6), 729–735. doi:10.1016/j.sleep.2015.02.537

de Leeuw, R., Colin, E. M., Dunnebier, E. A., & Mirmiran, M. (1991). Physiological effects of kangaroo care in very small preterm infants. *Biology of the Neonate, 59*(3), 149–155. doi:10.1159/000243337

Del Rio-Bermudez, C., & Blumberg, M. S. (2018). Active sleep promotes functional connectivity in developing sensorimotor networks. *Bioessays, 40*(4), e1700234. doi:10.1002/bies.201700234

Denenberg, V. H., & Thoman, E. B. (1981). Evidence for a functional role for active (REM) sleep in infancy. *Sleep, 4*(2), 185–191. doi:10.1093/sleep/4.2.185

Dereymaeker, A., Pillay, K., Vervisch, J., Van Huffel, S., Naulaers, G., Jansen, K., & De Vos, M. (2017). An automated quiet sleep detection approach in preterm infants as a gateway to assess brain maturation. *International Journal of Neural Systems, 27*(6), 1750023. doi:10.1142/S012906571750023X

Dieter, J. N., Field, T., Hernandez-Reif, M., Emory, E. K., & Redzepi, M. (2003). Stable preterm infants gain more weight and sleep less after five days of massage therapy. *Journal of Pediatric Psychology, 28*(6), 403–411. doi:10.1093/jpepsy/jsg030

DiPietro, J. A., Hodgson, D. M., Costigan, K. A., Hilton, S. C., & Johnson, T. R. (1996). Fetal neurobehavioral development. *Child Development, 67*(5), 2553–2567. doi:10.2307/1131640

Ditzenberger, G., Blackburn, S., Brown, B., & Altimier, L. (2016). Neurologic system. In C. L. Kenner & J. Wright (Eds.), *Neonatal nursing care handbook: An evidence-based approach to conditions and procedures* (2nd ed., pp. 83–172). New York, NY: Springer Publishing Company.

Dmowska, A., Andrews, B., Schreiber, M., & Msall, M. E. (2016). Implementing community supports to lessen health disparities at kindergarten entry for very preterm survivors. *International Journal of Child Health and Human Development, 9*(4), 535–544.

Dorn, F., Wirth, L., Gorbey, S., Wege, M., Zemlin, M., Maier, R. F., & Lemmer, B. (2014). Influence of acoustic stimulation on the circadian and ultradian rhythm of premature infants. *Chronobiology International, 31*(9), 1062–1074. doi:10.3109/07420528.2014.948183

dos Santos, A. Á., Khan, R. L., Rocha, G., & Nunes, M. L. (2014). Behavior and EEG concordance of active and quiet sleep in preterm very low birth weight and full-term neonates at matched conceptional age. *Early Human Development, 90*(9), 507–510. doi:10.1016/j.earlhumdev.2014.06.014

Dubois, J., Dehaene-Lambertz, G., Kulikova, S., Poupon, C., & Hu, P. S. (2014). The early development of brain white matter: A review of imaging studies in fetuses, newborns and infants. *Neuroscience, 276*, 48–71. doi:10.1016/j.neuroscience.2013.12.044

Dubowitz, L., Ricciw, D., & Mercuri, E. (2005). The Dubowitz neurological examination of the full-term newborn. *Mental Retardation and Developmental Disabilities Research Review, 11*(1), 52–60. doi:10.1002/mrdd.20048

Duffy, F. H., Als, H., & McAnulty, G. B. (1990). Behavioral and electrophysiological evidence for gestational age effects in healthy preterm and full-term infants studied two weeks after expected due date. *Child Development, 61*(4), 271–286. doi:10.2307/1130893

du Plessis, A. J., Limperopoulos, C., & Volpe, J. J. (2018). Cerebellar development. In J. J. Volpe, T. E. Inder, B. T. Darras, L. S. de Vries, A. J. du Plessis, J. J. Neil, & J. M. Perlman (Eds.), *Volpe's neurology of the newborn* (6th ed., pp. 73–99). Philadelphia, PA: Elsevier.

du Plessis, A. J., & Volpe, J. J. (2018). Neural tube development. In J. J. Volpe, T. E. Inder, B. T. Darras, L. S. de Vries, A. J. du Plessis, J. J. Neil, & J. M. Perlman (Eds.), *Volpe's neurology of the newborn* (6th ed., pp. 3–33). Philadelphia, PA: Elsevier.

Duxbury, M. L., Henly, S. J., Broz, L. J., Armstrong, G. D., & Wachdorf, C. M. (1984). Caregiver disruptions and sleep of high-risk infants. *Heart and Lung*, *13*(2), 141–147.

Eckerman, C. O., Oehler, J. M., Medvin, M. B., & Hannan, T. E. (1994). Premature newborns as social partners before term age. *Infant Behavior and Development*, *17*(1), 55–70. doi:10.1016/0163-6383(94)90022-1

Einspieler, C., & Prechtl, H. (2005). Prechtl's assessment of general movements: A diagnostic tool for the functional assessment of the young nervous system. *Mental Retardation and Developmental Disabilities Research Review, 11*, 61–70. doi:10.1002/mrdd.20051

Elder, D. E., Campbell, A. J., Larsen, P. D., & Galletly, D. (2011). Respiratory variability in preterm and term infants: Effect of sleep state, position and age. *Respiratory Physiology and Neurobiology, 175*(2), 234–238. doi:10.1016/j.resp.2010.11.011

Elder, D. E., Larsen, P. D., Galletly, D., & Campbell, A. J. (2010). Cardioventilatory coupling in preterm and term infants: Effect of position and sleep state. *Respiratory Physiology and Neurobiology, 174*(1\2), 128–134. doi:10.1016/j.resp.2010.05.012

El-Dib, M., Massaro, A. N., Glass, P., & Aly, H. (2011). Neurodevelopmental assessment of the newborn: An opportunity for prediction of outcome. *Brain Development, 33*(2), 95–105. doi:10.1016/j.braindev.2010.04.004

El-Dib, M., Massaro, A. N., Glass, P., & Aly, H. (2014). Sleep wake cycling and neurodevelopmental outcome in very low birth weight infants. *Journal of Maternal-Fetal and Neonatal Medicine, 27*(9), 892–897. doi:10.3109/14767058.2013.845160

ElHassan, N. O., Bai, S., Gibson, N., Holland, G., Robbins, J. M., & Kaiser, J. R. (2018). The impact of prematurity and maternal socioeconomic status and education level on achievement-test scores up to 8th grade. *PLoS One, 13*(5), e0198083. doi:10.1371/journal.pone.0198083

Ellingson, R. J., & Peters, J. F. (1980). Development of EEG and daytime sleep patterns in low risk premature infants during the first year of life: Longitudinal observations. *Electroencephalography and Clinical Neurophysiology, 50*(1\2), 165–171. doi:10.1016/0013-4694(80)90333-8

Faas, A. E. (2013). Neonatal responsiveness to the odor of amniotic fluid. *Archivos Argentinos De Pediatria, 111*(2), 105–109. doi:10.1590/S0325-00752013000200004

Fajardo, B., Browning, M., Fisher, D., & Paton, J. (1990). Effect of nursery environment on state regulation in very-low-birth-weight premature infants. *Infant Behavior and Development, 13*(3), 287–303. doi:10.1016/0163-6383(90)90036-8

Farooqi, A., Hägglöf, B., Sedin, G., & Serenius, F. (2011). Impact at age 11 years of major neonatal morbidities in children born extremely preterm. *Pediatrics, 127*(5), e1247–e1257. doi:10.1542/peds.2010-0806

Fearon, I., Kisilevsky, B. S., Hains, S. M., Muir, D. W., & Tranmer, J. (1997). Swaddling after heel lance: Age-specific effects on behavioral recovery in preterm infants. *Journal of Developmental and Behavioral Pediatrics, 18*, 222–232. Retrieved from https://journals.lww.com/jrnldbp/Abstract/1997/08000/Swaddling_After_Heel_Lance__Age_Specific_Effects.2.aspx

Feldman, R. (2006). From biological rhythms to social rhythms: Physiological precursors of mother-infant synchrony. *Developmental Psychology, 42*(1), 175–188. doi:10.1037/0012-1649.42.1.175

Feldman, R., & Eidelman, A. I. (2003). Skin-to-skin contact (kangaroo care) accelerates autonomic and neurobehavioural maturation in preterm infants. *Developmental Medicine and Child Neurology, 45*(4), 274–281. doi:10.1111/j.1469-8749.2003.tb00343.x

Feldman, R., Rosenthal, Z., & Eidelman, A. I. (2014). Maternal-preterm skin-to-skin contact enhances child physiologic organization and cognitive control across the first 10 years of life. *Biological Psychiatry, 75*(1), 56–64. doi:10.1016/j.biopsych.2013.08.012

Ferrari, F., Torricelli, A., Giustardi, A., Benatti, A., Bolzani, R., Ori, L., & Frigieri, G. (1992). Bioelectric maturation in full-term infants and in healthy and pathological preterm infants at term post-menstrual age. *Early Human Development, 28*(1), 37–63. doi:10.1016/0378-3782(92)90006-3

Fewell, J. E., & Baker, S. B. (1987). Arousal from sleep during rapidly developing hypoxemia in lambs. *Pediatric Research, 22*(4), 471–477. doi:10.1203/00006450-198710000-00023

Field, T., Diego, M., & Hernandez-Reif, M. (2011). Potential underlying mechanisms for greater weight gain in massaged preterm infants. *Infant Behavior and Development, 34*(3), 383–389. doi:10.1016/j.infbeh.2010.12.001

Field, T., Diego, M. A., Hernandez-Reif, M., Deeds, O., & Figuereido, B. (2006). Moderate versus light pressure massage therapy leads to greater weight gain in preterm infants. *Infant Behavior and Development, 29*(4), 574–578. doi:10.1016/j.infbeh.2006.07.011

Field, T., Hernandez-Reif, M., Diego, M., Feijo, L., Vera, Y., & Gil, K. (2004). Massage therapy by parents improves early growth and development. *Infant Behavior and Development*, *27*(4), 435–442. doi:10.1016/j.infbeh.2004.03.004

Figueiredo, B., Dias, C. C., Pinto, T. M., & Field, T. (2017). Exclusive breastfeeding at three months and infant sleep-wake behaviors at two weeks, three and six months. *Infant Behavior and Development, 49*, 62–69. doi:10.1016/j.infbeh.2017.06.006

Fink, A., Bronas, U., & Calik, M. (2018). Autonomic regulation during sleep and wakefulness: A review with implications for defining the pathophysiology of neurological disorders. *Clinical Autonomic Research, 28*(6), 509–518. doi:10.1007/s10286-018-0560-9

Fiori, S., & Guzzetta, A. (2015). Plasticity following early-life brain injury: Insights from quantitative MRI. *Seminars in Perinatology, 39*(2), 141–146. doi:10.1053/j.semperi.2015.01.007

Fleiss, B. H. S., Mezger, V., & Gressens, P. (2018). Central nervous system development. In C. A. Gleason & S. E. Juul (Eds.), *Avery's diseases of the newborn* (10th ed., pp. 852–856). Philadelphia, PA: Elsevier.

Flohr, E., Boesveldt, S., Haehner, A., Iannilli, E., Sinding, C., & Hummel, T. (2015). Time-course of trigeminal versus olfactory stimulation: Evidence from chemosensory evoked potentials. *International Journal of Psychophysiology, 95*(3), 388–394. doi:10.1016/j.ijpsycho.2015.01.014

Foreman, S. W., Thomas, K. A., & Blackburn, S. T. (2008). Individual and gender differences matter in preterm infant state development. *Journal of Obstetric, Gynecologic, and Neonatal Nursing, 37*(6), 657–665. doi:10.1111/j.1552-6909.2008.00292.x

Foster, J., Psaila, K., & Patterson, T. (2016). Non-nutritive sucking for increasing physiologic stability and nutrition in preterm infants. *Cochrane Database of Systematic Reviews,* (10), CD001071. doi:10.1002/146518 58.CD001071.pub3

Franck, L. S. (1987). A national survey of the assessment and treatment of pain and agitation in the neonatal intensive care unit. *Journal of Obstetric, Gynecologic, and Neonatal Nursing*, *16*(6), 387–393. doi:10.1111/j.1552-6909.1987.tb01599.x

Freedman, K., Radhakrishna, S., Escanilla, O., & Linster, C. (2013). Duration and specificity of olfactory nonassociative memory. *Chemical Senses, 38*(4), 369–375. doi:10.1093/chemse/bjt010

Frie, J., Bartocci, M., Lagercrantz, H., & Kuhn, P. (2018). Cortical responses to alien odors in newborns: An fNIRS study. *Cerebral Cortex, 28*(9), 3229–3240. doi:10.1093/cercor/bhx194

Fuller, B. F. (1991). Acoustic discrimination of three types of infant cries. *Nursing Research*, *40*(3), 156–160. doi:10.1097/00006199-199105000-00007

Fyfe, K. L., Yiallourou, S. R., Wong, F. Y., Odoi, A., Walker, A. M., & Horne, R. S. (2014). Cerebral oxygenation in preterm infants. *Pediatrics, 134*(3), 435–445. doi:10.1542/peds.2014-0773

Gabriel, M., Grote, B., & Jonas, M. (1981). Sleep-wake pattern in preterm infants under two different care schedules during four-day polygraphic recording. *Neuropediatrics, 12*(4), 366–373. doi:10.1055/s-2008-1059667

Galland, B. C., Hayman, R. M., Taylor, B. J., Bolton, D. P. G., Sayers, R. M., & Williams, S. M. (2000). Factors affecting heart rate variability and heart rate responses to tilting in infants aged 1 and 3 months. *Pediatric Research, 48*, 360–368. doi:10.1203/00006450-200009000-00017

Gao, W., Lin, W., Grewen, K., & Gilmore, J. H. (2017). Functional connectivity of the infant human brain: Plastic and modifiable. *The Neuroscientist, 23*, 169–184. doi:10.1177/1073858416635986

Gaultier, C. (1990). Respiratory adaptation during sleep in infants. *Lung, 168*(Suppl. 1), 905–911. doi:10.1007/BF02718226

Gaultier, C. L. (1994). Apnea and sleep state in newborns and infants. *Biology of the Neonate, 65*(3\4), 231–234. doi:10.1159/000244057

Gerard, C. M., Harris, K. A., & Thach, B. T. (2002). Spontaneous arousals in supine infants while swaddled and unswaddled during rapid eye movement and quiet sleep. *Pediatrics*, *110*(6), e70. doi:10.1542/peds.110.6.e70

Gertner, S., Greenbaum, C. W., Sadeh, A., Dolfin, Z., Sirota, L., & Ben-Nun, Y. (2002). Sleep-wake patterns in preterm infants and 6 month's home environment: Implications for early cognitive development. *Early Human Development*, *68*(2), 93–102. doi:10.1016/S0378-3782(02)00018-X

Ghorbani, F., Asadollahi, M., & Valizadeh, S. (2013). Comparison the effect of sleep positioning on cardiorespiratory rate in noninvasive ventilated premature infants. *Nursing and Midwifery Studies, 2*(2), 182–187. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4228557

Glass, H.C., Costarino, A.T., Stayer, S.A., Brett, C., Cladis, F., Davis, P.J. (2015). Outcomes for Extremely Premature Infants. *Anesthesia and analgesia,120*(6), 1337–1351. doi:10.1213/ANE.0000000000000705

Gorzilio, D. M., Garrido, E., Gaspardo, C. M., Martinez, F. E., & Linhares, M. B. (2015). Neurobehavioral development prior to term-Age of preterm infants and acute stressful events during neonatal hospitalization. *Early Human Development, 91*(12), 769–775. doi:10.1016/j.earlhumdev.2015.09.003

Gottfried, A. W. (1985). Environment of newborn infants in special care units. In A. W. Gottfried & J. L. Gaiter (Eds.), *Infant stress under intensive care: Environmental neonatology* (pp. 23–54). Baltimore, MD: University Park Press.

Graven, S. N. (2011). Early visual development: Implications for the neonatal intensive care unit and care. *Clinics in Perinatology, 38*(4), 671–683. doi:10.1016/j.clp.2011.08.006

Graven, S. N., & Browne, J. V. (2008). Sensory development in the fetus, neonate, and infant: Introduction and overview. *Newborn and Infant Nursing Reviews, 8*(4), 169–172. doi:10.1053/j.nainr.2008.10.007

Greene, M. M., Rossman, B., Patra, K., Kratovil, A., Janes, J., & Meier, P. (2015). Depression, anxiety, and perinatal-specific posttraumatic distress in mothers of very low birth weight infants in the neonatal intensive care unit. *Journal of Developmental and Behavioral Pediatrics, 36*(5), 362–370. doi:10.1097/DBP.0000000000000174

Greene, Z., O'Donnell, C. P., & Walshe, M. (2016). Oral stimulation for promoting oral feeding in preterm infants. *Cochrane Database of Systematic Reviews,* (9), CD009720. doi:10.1002/14651858.CD009720.pub2

Greisen, G., Hellstrom-Vestas, L., Lou, H., Rosen, I., & Svenningsen, N. (1985). Sleep-waking shifts and cerebral blood flow in stable preterm infants. *Pediatric Research, 19*(11), 1156–1159. doi:10.1203/00006450-198511000-00008

Gressens, P., & Huppi, P. S. (2015). Normal and abnormal brain development. In R. J. Martin, A. A. Fanaroff, & M. C. Walsh (Eds.), *Fanaroff and Martin's neonatal-perinatal medicine: Diseases of the fetus and infant* (8th ed., pp. 836–865). Philadelphia, PA: Elsevier.

Griffith, T., Rankin, K., & White-Traut, R. (2017). The relationship between behavioral states and oral feeding efficiency in preterm infants. *Advances in Neonatal Care, 17*(1), E12–E19. doi:10.1097/ANC.0000000000000318

Grunau, R. V., & Craig, K. D. (1987). Pain expression in neonates: Facial action and cry. *Pain, 28*(3), 395–410. doi:10.1016/0304-3959(87)90073-X

Guyer, C., Huber, R., Fontijn, J., Bucher, H. U., Nicolai, H., Werner, H., . . . Jenni, O. G. (2012). Cycled light exposure reduces fussing and crying in very preterm infants. *Pediatrics, 130*(1), e145–e151. doi:10.1542/peds.2011-2671

Guyer, C., Huber, R., Fontijn, J., Bucher, H. U., Nicolai, H., Werner, H., . . . Jenni, O. G. (2015). Very preterm infants show earlier emergence of 24-hour sleep-wake rhythms compared to term infants. *Early Human Development, 91*(1), 37–42. doi:10.1016/j.earlhumdev.2014.11.002

Guyer, A., Pérez-Edgar, K., & Crone, E. (2018). Opportunities for neurodevelopmental plasticity from infancy through early adulthood. *Child Development, 89*(3), 687–697. doi:10.1111/cdev.13073

Guzzetta, A., D'Acunto, M. G., Carotenuto, M., Berardi, N., Bancale, A., Biagioni, E., . . . Cioni, G. (2011). The effects of preterm infant massage on brain electrical activity. *Developmental Medicine and Child Neurology*, *53*(Suppl. 4), 46–51. doi:10.1111/j.1469-8749.2011.04065.x

Hahn, J. S., & Tharp, B. R. (1990). The dysmature EEG pattern in infants with bronchopulmonary dysplasia and its prognostic implications. *Electroencephalography and Clinical Neurophysiology, 76*(2), 106–113. doi:10.1016/0013-4694(90)90208-2

Hall, E., & Greenberg, J. (2016). Estimating community-level costs of preterm birth. *Public Health, 141*, 222–228. doi:10.1016/j.puhe.2016.09.033

Hand, I. L., Noble, L., Wilks, M., Towler, E., Kim, M., & Yoon, J. J. (2004). Hering-Breuer reflex and sleep state in the preterm infant. *Pediatric Pulmonology, 37*(1), 61–64. doi:10.1002/ppul.10394

Harrison, L. L., Leeper, J., & Yoon, M. (1991). Preterm infants' physiologic responses to early parent touch. *Western Journal of Nursing Research, 13*(6), 698–713. doi:10.1177/019394599101300603

Harrison, L. L., Oliveet, L., Cunningham, K., Bodin, M. B., & Hicks, C. (1996). Effects of gentle human touch on preterm infants: Pilot study results. *Neonatal Network*, *15*(2), 35–42.

Harrison, L. L., Williams, A. K., Berbaum, M. L., Stem, J. T., & Leeper, J. (2000). Physiologic and behavioral effects of gentle human touch on preterm infants. *Research in Nursing and Health, 23*(6), 435–446. doi:10.1002/1098-240X(200012)23:6%3C435::AID-NUR3%3E3.0.CO;2-P

Hayes, M. J., Akilesh, M. R., Fukumizu, M., Gilles, A. A., Sallinen, B. A., Troese, M., & Paul, J. A. (2007). Apneic preterms and methylxanthines: Arousal deficits, sleep fragmentation and suppressed spontaneous movements. *Journal of Perinatology, 27*(12), 782–789. doi:10.1038/sj.jp.7211820

Hayward, K. M., Johnston, C. C., Campbell-Yeo, M. L., Price, S. L., Houk, S. L., Whyte, R. K., . . . Caddell, K. E. (2015). Effect of cobedding twins on coregulation, infant state, and twin safety. *Journal of Obstetric, Gynecologic, and Neonatal Nursing, 44*(2), 193–202. doi:10.1111/1552-6909.12557

Heraghty, J. L., Hilliard, T. N., Henderson, A. J., & Fleming, P. J. (2008). The physiology of sleep in infants. *Archives of Disease in Childhood, 93*(11), 982–985. doi:10.1136/adc.2006.113290

High, P. C., & Gorski, P. A. (1985). Recording environmental influences on infant development in the intensive care nursery: Womb for improvement. In A. W. Gottfried & J. L. Gaiter (Eds.), *Infant stress under intensive care: Environmental neonatology* (pp. 131–155). Baltimore, MD: University Park Press.

Hofer, M. (2010). Hidden regulators within the mother-infant interaction. In Lester, B. M., & Sparrow, J. D. (Eds.), *Nurturing children and families: Building on the legacy of T. Berry Brazelton*. Hoboken, NJ: Wiley-Blackwell Publishing.

Holditch-Davis, D. (1990). The development of sleeping and waking states in high-risk preterm infants. *Infant Behavior and Development, 13*(4), 513–531. doi:10.1016/0163-6383(90)90020-9

Holditch-Davis, D. (1995). Behaviors of preterm infants with and without chronic lung disease when alone and when with nurses. *Neonatal Network*, *14*(7), 51–57.

Holditch-Davis, D., Barham, L. N., O'Hale, A., & Tucker, B. (1995). The effect of standardized rest periods on convalescent preterm infants. *Journal of Obstetric, Gynecologic, and Neonatal Nursing, 24*(5), 424–432. doi:10.1111/j.1552-6909.1995.tb02499.x

Holditch-Davis, D., Belyea, M., & Edwards, L. (2005). Prediction of 3-year developmental outcomes from sleep development over the preterm period. *Infant Behavior and Development, 28*(2), 118–131. doi:10.1016/j.infbeh.2004.12.001

Holditch-Davis, D., Brandon, D. H., & Schwartz, T. (2003). Development of behaviors in preterm infants: Relation to sleeping and waking. *Nursing Research, 52*(5), 307–317. doi:10.1016/j.infbeh.2004.12.001

Holditch-Davis, D., & Calhoun, M. (1989). Do preterm infants show behavioral responses to painful procedures? In S. G. Funk, E. M. Tornquist, M. T. Champagne, L. A. Copp, & R. A. Wiese (Eds.), *Key aspects of comfort: Management of pain, fatigue, and nausea* (pp. 35–43). New York, NY: Springer Publishing Company.

Holditch-Davis, D., & Edwards, L. (1998a). Modeling development of sleep-wake behaviors: II. Results of 2 cohorts of preterms. *Physiology and Behavior, 63*(3), 319–328. doi:10.1016/S0031-9384(97)00396-X

Holditch-Davis, D., & Edwards, L. (1998b). Temporal organization of sleep-wake states in preterm infants. *Developmental Psychobiology, 33*(3), 257–269. doi:10.1002/(SICI)1098-2302(199811)33:3%3C257::AID-DEV6%3E3.0.CO;2-Q

Holditch-Davis, D., & Hudson, D. C. (1995). Using preterm infant behaviors to identify acute medical complications. In S. G. Funk, E. M. Tornquist, M. T. Champagne, & R. A. Wiese (Eds.), *Key aspects of caring for the acutely ill: Technological aspects, patient education, and quality of life* (pp. 95–120). New York, NY: Springer Publishing Company.

Holditch-Davis, D., & Lee, D. A. (1993). The behaviors and nursing care of preterm infants with chronic lung disease. In S. G. Funk, E. M. Tornquist, M. T. Champagne, & R. A. Wiese (Eds.), *Key aspects of caring for the chronically ill: Hospital and home* (pp. 250–270). New York, NY: Springer Publishing Company.

Holditch-Davis, D., Miles, M., & Belyea, M. (2000). Feeding and non-feeding interactions of mothers and premature infants. *Western Journal of Nursing Research*, *22*(3), 320–334. doi:10.1177/01939450022044449

Holditch-Davis, D., Scher, M., & Schwartz, T. (2004). Respiratory development in preterm infants. *Journal of Perinatology, 24*(10), 631–639. doi:10.1038/sj.jp.7211150

Holditch-Davis, D., Scher, M., Schwartz, T., & Hudson-Barr, D. (2004). Sleeping and waking state development in preterm infants. *Early Human Development, 80*(1), 43–64. doi:10.1016/j.earlhumdev.2004.05.006

Holditch-Davis, D., Tesh, E. M., Burchinal, M., & Miles, M. S. (1999). Early interactions between mothers and their medically fragile infants. *Applied Developmental Science*, *3*(3), 155–167. doi:10.1207/s1532480xads0303_2

Holditch-Davis, D., & Thoman, E. B. (1987). Behavioral states of premature infants: Implications for neural and behavioral development. *Developmental Psychobiology, 20*(1), 25–38. doi:10.1002/dev.420200107

Holmes, D. L., Nagy, J. N., Slaymaker, F., Sosnowski, R. J., Prinz, S. M., & Pasternak, J. F. (1982). Early influences of prematurity, illness, and prolonged hospitalization on infant behavior. *Developmental Psychology, 18*(5), 744–750. doi:10.1037/0012-1649.18.5.744

Holsti, A., Serenius, F., & Farooqi, A. (2018). Impact of major neonatal morbidities on adolescents born at 23-25 weeks of gestation. *Acta Pμdiatrica, 107*(11), 1893–1901. doi:10.1111/apa.14445

Hooker, D. (1952). Early human fetal activity. *The Anatomical Record, 113*(4), 503–504. doi:10.1002/ar.1091130411

Horne, R. S. C., Sun, S., Yiallourou, S. R., Fyfe, K. L., Odoi, A., & Wong, F. Y. (2018). Comparison of the longitudinal effects of persistent periodic breathing and apnoea on cerebral oxygenation in term- and preterm-born infants. *Journal of Physiology, 596*(23), 6021–6031. doi:10.1113/JP275686

Huang, Y. S., Paiva, T., Hsu, J. F., Kuo, M. C., & Guilleminault, C. (2014). Sleep and breathing in premature infants at 6 months post-natal age. *BMC Pediatrics, 14*, 303. doi:10.1186/s12887-014-0303-6

Huntington, L., Hans, S., & Zeskind, P. S. (1990). The relations among cry characteristics, demographic variables, and developmental test scores in infants prenatally exposed to methadone. *Infant Behavior and Development*, *13*(4), 533–538. doi:10.1016/0163-6383(90)90021-Y

Hwang, S. S., Smith, R. A., Barfield, W. D., Smith, V. C., McCormick, M. C., & Williams, M. A. (2016). Supine sleep positioning in preterm and term infants after hospital discharge from 2000 to 2011. *Journal of Perinatology*, 36(9), 787–793. doi:10.1038/jp.2016.80

Hyman, C., Snider, L. M., Majnemer, A., & Mazer, B. (2005). Concurrent validity of the Neurobehavioural Assessment for Pre-term Infants (NAPI) at term age. *Pediatric Rehabilitation, 8*(3), 225–234. doi:10.1080/13638490400022220

Im, H., & Kim, E. (2009). Effect of Yakson and Gentle Human Touch versus usual care on urine stress hormones and behaviors in preterm infants: A quasi-experimental study. *International Journal of Nursing Studies, 46*(4), 450–458. doi:10.1016/j.ijnurstu.2008.01.009

Im, H., Kim, E., & Cain, K. C. (2009). Acute effects of Yakson and Gentle Human Touch on the behavioral state of preterm infants. *Journal of Child Health Care, 13*(3), 212–226. doi:10.1177/1367493509337441

Ingersoll, E. W., & Thoman, E. B. (1994). The breathing bear: Effects on respiration in premature infants. *Physiology and Behavior*, *56*(5), 855–859. doi:10.1177/1367493509337441

Ingersoll, E. W., & Thoman, E. B. (1999). Sleep/wake states of preterm infants: Stability, developmental change, diurnal variation, and relation with caregiving activity. *Child Development, 70*(1), 1–10. doi:10.1111/1467-8624.00001

Inguaggiato, E., Sgandurra, G., & Cioni, G. (2017). Brain plasticity and early development: Implications for early intervention in neurodevelopmental disorders. *Neuropsychiatrie De L'enfance Et De L'adolescence, 65*(5), 299–306. doi:10.1016/j.neurenf.2017.03.009

Jarus, T., Bart, O., Rabinovich, G., Sadeh, A., Bloch, L., Dolfin, T., & Litmanovitz, I. (2011). Effects of prone and supine positions on sleep state and stress responses in preterm infants. *Infant Behavior and Development, 34*(2), 257–263. doi:10.1016/j.infbeh.2010.12.014

Jeremy, R. J., & Hans, S. L. (1985). Behavior of neonates exposed in utero to methadone as assessed on the Brazelton Scale. *Infant Behavior and Development, 8*(3), 323–336. doi:10.1016/0163-6383(85)90021-9

Jiang, C.-M., Yang, Y.--H., Chen, L.-Q., Shuai, X.-H., Lu, H., Xiang, J.-H., . . . Huang, X.-M. (2015). Early amplitude-integrated EEG monitoring 6 h after birth predicts long-term neurodevelopment of asphyxiated late preterm infants. *European Journal of Pediatrics, 174*(8), 1043–1052. doi:10.1007/s00431-015-2490-z

Jiang, Z. D., & Chen, C. (2014). Impaired neural conduction in the auditory brainstem of high-risk very preterm infants. *Clinical Neurophysiology, 125*, 1231–1237. doi: 10.1016/j.clinph.2013.11.012

Johnson, S., & Marlow, N. (2011). Preterm birth and childhood psychiatric disorders. *Pediatric Research, 69*, 11R–18R. doi:10.1203/PDR.0b013e318212faa0

Johnston, C. C., Sherraud, A., Stevens, B., Franck, L., Stremler, R., & Jack, A. (1999). Do cry features reflect pain intensity in preterm neonates? *Biology of the Neonate, 76*, 120–124. doi:10.1159/000014150

Johnston, C. C., Stevens, B. J., Franck, L. S., Jack, A., Stremler, R., & Platt, R. (1999). Factors explaining lack of response to heelstick in preterm newborns. *Journal of Obstetric, Gynecologic, and Neonatal Nursing, 28*, 587–594. doi:10.1111/j.1552-6909.1999.tb02167.x

Johnston, C. C., Stremler, R., Stevens, B., & Horton, L. (1997). Effectiveness of oral sucrose and simulated rocking on pain response in preterm neonates. *Pain*, *72*(1), 193–199. doi:10.1016/S0304-3959(97)00033-X

Juul, S. E., Fleiss, B., McAdams, R. M., & Gressens, P. (2018). Neuroprotection strategies for the newborn. In C. A. Gleason & S. E. Judd (Eds.), *Avery's diseases of the newborn* (10th ed., pp. 910–921). Philadelphia, PA: Elsevier.

Kaffashi, F., Scher, M. S., Ludington-Hoe, S. M., & Loparo, K. A. (2013). An analysis of the kangaroo care intervention using neonatal EEG complexity: A preliminary study. *Clinical Neurophysiology, 124*(2), 238–246. doi:10.1016/j.clinph.2012.06.021

Kamhawy, H., Holditch-Davis, D., Alsharkawy, S., Alrafay, S., & Corazzini, K. (2014). Non-nutritive sucking for preterm infants in Egypt. *Journal of Obstetric, Gynecologic, and Neonatal Nursing, 43*(3), 330–340. doi:10.1111/1552-6909.12310

Kaneshi, Y., Ohta, H., Morioka, K., Hayasaka, I., Uzuki, Y., Akimoto, T., . . . Minakami, H. (2016). Influence of light exposure at nighttime on sleep development and body growth of preterm infants. *Scientific Reports, 6,* 21680. doi:10.1038/srep21680

Karch, D., Rothe, R., Jurisch, R., Heldt-Hilderbrandt, R., Lübbesmeier, A., & Lemburg, P. (1982). Behavioural changes and bioelectric brain maturation of preterm and fullterm newborn infants: A polygraphic study. *Developmental Medicine and Child Neurology, 24*(1), 30–47. doi:10.1111/j.1469-8749.1982.tb13580.x

Khalesi, N., Khosravi, N., Ranjbar, A., Godarzi, Z., & Karimi, A. (2017). The effectiveness of earmuffs on the physiologic and behavioral stability in preterm infants. *International Journal of Pediatric Otorhinolaryngology, 98*, 43–47. doi:10.1016/j.ijporl.2017.04.028

Kinney, H. C., & Volpe, J. J. (2018a). Myelination events. In J. J. Volpe, T. E. Inder, B. T. Darras, L. S. de Vries, A. J. du Plessis, J. J. Neil, & J. M. Perlman (Eds.), *Volpe's neurology of the newborn* (6th ed., pp. 176–188). Philadelphia, PA: Elsevier.

Kinney, H. C., & Volpe, J. J. (2018b). Organizational events. In J. J. Volpe, T. E. Inder, B. T. Darras, L. S. de Vries, A. J. du Plessis, J. J. Neil, & J. M. Perlman (Eds.), *Volpe's neurology of the newborn* (6th ed., pp. 145–175). Philadelphia, PA: Elsevier.

Kisilevsky, B. S. (2016). Fetal auditory processing: Implications for language development? In N. Reissland & B. S. Kisilevsky (Eds.), *Fetal development: Research on brain and behavior, environmental influences, and emerging technologies* (pp. 133–154). Cham, Switzerland: Springer.

Kisilevsky, B. S., Gilmour, A., Stutzman, S. S., Hains, S. M. J., & Brown, C. A. (2012). Atypical fetal response to the mother's voice in diabetic compared with overweight pregnancies. *Journal of Developmental and Behavioral Pediatrics: JDBP, 33*(1), 55–61. doi:10.1097/DBP.0b013e31823e791e

Kisilevsky, B. S., Muir, D. W., & Low, J. A. (1992). Maturation of human fetal responses to vibroacoustic stimulation. *Child Development, 63*(6), 1497–1508. doi:10.1111/j.1467-8624.1992.tb01710.x

Kitase, Y., Sato, Y., Takahashi, H., Shimizu, M., Ishikawa, C., Yamamoto, H., & Hayakawa, M. (2017). A new type of swaddling clothing improved development of preterm infants in neonatal intensive care units. *Early Human Development, 112*, 25–28. doi:10.1016/j.earlhumdev.2017.06.005

Kohyama, J., & Iwakawa, Y. (1990). Developmental changes in phasic sleep parameters as reflections of the brain-stem maturation: Polysomnographic examinations of infants, including premature neonates. *Electroencephalography and Clinical Neurophysiology, 76*(4), 325–330. doi:10.1016/0013-4694(90)90033-G

Koolen, N., Oberdorfer, L., Rona, Z., Giordano, V., Werther, T., Klebermass-Schrehof, K., . . . Vanhatalo S. (2017). Automated classification of neonatal sleep states using EEG. *Clinical Neurophysiology, 128*(6), 1100–1108. doi:10.1016/j.clinph.2017.02.025

Korner, A. F. (1972). State as variable, obstacle, and as mediator of stimulation in infant research. *Merrill-Palmer Quarterly, 18*(2), 77–94. Retrieved from https://www.jstor.org/stable/23083964

Korner, A. F., & Constantinou, J. C. (2001). *The neurobehavioral assessment of the preterm infant: Reliability and developmental and clinical validity.* New York, NY: Guilford Press.

Korner, A. F., Constantinou, J. C., Dimiceli, S., Brown, B. W., & Thom, V. A.(1991). Establishing the reliability and developmental validity of a neurobehavioral assessment for preterm infants: A methodological process. *Child Development, 62*(5), 1200–1208. doi:10.2307/1131163

Korotchikova, I., Stevenson, N. J., Livingstone, V., Ryan, C. A., & Boylan, G. B. (2016). Sleep-wake cycle of the healthy term newborn infant in the immediate postnatal period. *Clinical Neurophysiology, 127*(4), 2095–2101. doi:10.1016/j.clinph.2015.12.015

Kuhn, P., Zores, C., Astruc, D., Dufour, A., & Casper, C. (2011). Sensory system development and the physical environment of infants born very preterm. *Acta Paediatrica*, *18*(Suppl. 2), S92–S102. doi:10.1016/S0929-693X(11)71097-1

Kuhn, P., Zores, C., Langlet, C., Escande, B., Astruc, D., & Dufour, A. (2013). Moderate acoustic changes can disrupt the sleep of very preterm infants in their incubators. *Acta Paediatrica, 102*(10), 949–954. doi:10.1111/apa.12330

Kuhn, P., Zores, C., Pebayle, T., Hoeft, A., Langlet, C., Escande, B., . . . Dufour, A. (2012). Infants born very preterm react to variations of the acoustic environment in their incubator from a minimum signal-to-noise ratio threshold of 5 to 10 dBA. *Pediatric Research, 71*(4 Pt 1), 386–392. doi:10.1038/pr.2011.76

Lagercrantz, H., & Changeux, J. (2010). Basic consciousness of the newborn. *Seminars in Perinatology, 34*(3), 201–206. doi:10.1053/j.semperi.2010.02.004

Lahav, A., & Skoe, E. (2014). An acoustic gap between the NICU and womb: A potential risk for compromised neuroplasticity of the auditory system in preterm infants. *Frontiers in Neuroscience, 8*, 381. doi:10.3389/fnins.2014.00381

Lan, H.-Y., Yang, L., Hsieh, K.-H., Yin, T., Chang, Y.-C., & Liaw, J.-J. (2018). Effects of a supportive care bundle on sleep variables of preterm infants during hospitalization. *Research in Nursing and Health, 41*(3), 281–291. doi:10.1002/nur.21865

Lan, H.-Y., Yin, T., Chen, J.-L., Chang, Y.-C., & Liaw, J.-J. (2017). Factors associated with preterm infants' circadian sleep/wake patterns at the hospital. *Clinical Nursing Research, 28*(4), 456–472. doi:10.1177/1054773817724960

Lawhon, G., & Als, H. (2010). *Theoretical perspective for developmentally supportive care* (2nd ed.). Glenview, IL: National Association of Neonatal Nurses.

Lawhon, G., & Hedlund, R. E. (2008). Newborn individualized developmental care and assessment program training and education. *The Journal of Perinatal & Neonatal Nursing, 22*(2), 133–144. doi:10.1097/01.JPN.0000319100.90167.9f

Lawson, K. R., Turkewitz, G., Platt, M., & McCarton, C. (1985). Infant state in relation to its environmental context. *Infant Behavior and Development, 8*(3), 269–281. doi:10.1016/0163-6383(85)90016-5

Lee, H. J., Kim, H.-S., Kim, S.-Y., Sim, G. H., Kim, E. S., Choi, C. W., . . . Choi, J.-H. (2010). Effects of postnatal age and aminophylline on the maturation of amplitude-integrated electroencephalography

activity in preterm infants. *Neonatology, 98*(3), 245–253. doi:10.1159/000277936
Lee, H.-K. (2002). Effects of sponge bathing on vagal tone and behavioural responses in premature infants. *Journal of Clinical Nursing, 11*(4), 510–519. doi:10.1046/j.1365-2702.2002.00594.x
Lee, J., Kim, H.-S., Jung, Y. H., Choi, K. Y., Shin, S. H., Kim, E.-K., & Choi, J.-H. (2015). Oropharyngeal colostrum administration in extremely premature infants: An RCT,. *Pediatrics, 135*(2), e357–e366. doi:10.1542/peds.2014-2004
Lester, B. M., & Tronick, E. Z. (2004). History and description of the neonatal intensive care unit network neurobehavioral scale. *Pediatrics, 113*(Suppl. 2), 634–640. Retrieved from https://pediatrics.aappublications.org/content/113/Supplement_2/634
Lester, B. M., Tronick, E. Z., & Brazelton, T. B. (2004). The neonatal intensive care unit network neurobehavioral scale procedures. *Pediatrics, 113*(Suppl. 2), 641–667. Retrieved from https://pediatrics.aappublications.org/content/113/Supplement_2/641
Levesque, B. M., Pollack, P., Griffin, B. E., & Nielsen, H. C. (2000). Pulse oximetry: What's normal in the newborn nursery? *Pediatric Pulmonology, 30*(5), 406–412. doi:10.1002/1099-0496(200011)30:5%3C406::aid-ppul7%3E3.0.co;2-c
Liaw, J.-J., Yang, L., Lee, C.-M., Fan, H.-C., Chang, Y.-C., & Cheng, L.-P. (2013). Effects of combined use of non-nutritive sucking, oral sucrose, and facilitated tucking on infant behavioural states across heel-stick procedures: A prospective, randomised controlled trial. *International Journal of Nursing Studies, 50*(7), 883–894. doi:10.1016/j.ijnurstu.2012.08.021
Liaw, J.-J., Yang, L., Lo, C., Yuh, Y.-S., Fan, H.-C., Chang, Y.-C., & Chao, S.-C. (2012). Caregiving and positioning effects on preterm infant states over 24 hours in a neonatal unit in Taiwan. *Research in Nursing and Health, 35*(2), 132–145. doi:10.1002/nur.21458
Lickliter, R. (2011). The Integrated Development of Sensory Organization. *Clinics in Perinatology, 38*(4), 591–603. doi:10.1016/j.clp.2011.08.007
Limperopoulos, C. (2010). Extreme prematurity, cerebellar injury, and autism. *Seminars in Pediatric Neurology, 17*(1), 25–29. doi:10.1016/j.spen.2010.01.003
Lipchock, S. V., Reed, D. R., & Mennella, J. A. (2011). The gustatory and olfactory systems during infancy: Implications for development of feeding behaviors in the high-risk neonate. *Clinics in Perinatology, 38*(4), 627–641. doi:10.1016/j.clp.2011.08.008
Litt, J. S., Taylor, G. H., Margevicius, S., Schlucter, M., Andreias, L., & Hack, M. (2012). Academic achievement of adolescents born with extremely low birthweight. *Acta Paediatrica, 101*(12), 1240–1245. doi:10.1111/j.1651-2227.2012.02790.x
Liu, J., Zhang, A., & Li, L. (2012). Sleep duration and overweight/obesity in children: Review and implications for pediatric nursing. *Journal for Specialists in Pediatric Nursing, 17*(3), 193–204. doi:10.1111/j.1744-6155.2012.00332.x
Liu, W., Laudert, S., Perkins, B., MacMillan-York, E., Martin, S., & Graven, S. (2007). The development of potentially better practices to support the neurodevelopment of infants in the NICU. *Journal of Perinatology, 27*, S48–S74. doi:10.1038/sj.jp.7211844
Llaguno, N. S., Pedreira Mda, L., Avelar, A. F., Avena, M. J., Tsunemi, M. H., & Pinheiro, E. M. (2015). Polysomnography assessment of sleep and wakefulness in premature newborns. *Revista Brasileira de Enfermagem, 68*(6), 1109–1115. doi:10.1590/0034-7167.2015680616i
Lodrup, K. C., Mowinckel, P., & Carlsen, K. H. (1992). Lung function measurements in awake compared to sleeping newborn infants. *Pediatric Pulmonology, 12*(2), 99–104. doi:10.1002/ppul.1950120208
Loewy. J., Stewart, K., Dassler, A. M., Telsey, A., & Homel, P. (2013). The effects of music therapy on vital signs, feeding, and sleep in premature infants. *Pediatrics, 131*(5), 902–918. doi:10.1542/peds.2012-1367
Lorenz, L., Marulli, A., Dawson, J. A., Owen, L. S., Manley, B. J., Donath, S. M., . . . Kamlin, C. O. F. (2017). Cerebral oxygenation during skin-to-skin care in preterm infants not receiving respiratory support. *Archives of Disease in Childhood: Fetal and Neonatal Edition, 103*(2), F137–F142. doi:10.1136/archdischild-2016-312471
Louis, J., Cannard, C., Bastuji, H., & Challamel, M. J. (1997). Sleep ontogenesis revisited: A longitudinal 24-hour home polygraphic study on 15 normal infants during the first two years of life. *Sleep, 20*(5), 323–333. doi:10.1093/sleep/20.5.323
Ludington-Hoe, S. M., Johnson, M. W., Morgan, K., Lewis, T., Gutman, J., Wilson, P. D., & Scher, M. S. (2006). Neurophysiologic assessment of neonatal sleep organization: Preliminary results of a randomized, controlled trial of skin contact with preterm infants. *Pediatrics, 117*(5), e909–e923. doi:10.1542/peds.2004-1422
Luong, K. C., Nguyen, T. L., Thi, H. D. Y., Carrara, H. P. O., & Bergman, N. J. (2016). Newly born low birth weight infants stabilize better in skin-to-skin contact than when separated from their mothers: A randomized controlled trial. *Acta Paediatrica., 105*(4), 381–390. doi:10.1111/apa.13164
Maas, Y. G. H., Mirmiran, M., Hart, A. A., Koppe, J. G., Ariagno, R. L., & Spekreijse, H. (2000). Predictive value of neonatal neurological tests for developmental outcome of preterm infants. *Journal of Pediatrics, 137*(1), 100–106. doi:10.1067/mpd.2000.106901
Mäkelä, T. E., Peltola, M. J., Nieminen, P., Paavonen, E. J., Saarenpää-Heikkilä, O., Paunio, T., & Kylliäinen, A. (2018). Night awakening in infancy: Developmental stability and longitudinal associations with psychomotor development. *Developmental Psychology, 54*(7), 1208–1218. doi:10.1037/dev0000503
Mangham, L. J., Petrou, S., Doyle, L. W., Draper, E. S., & Marlow, N. (2009). The cost of preterm birth throughout childhood in England and Wales. *Pediatrics, 123*(2), e312–e327. doi:10.1542/peds.2008-1827
Marlow, N., Bennett, C., Draper, E. S., Hennessy, E. M., Morgan, A. S., & Costeloe, K. L. (2014). Perinatal outcomes for extremely preterm babies in relation to place of birth in England: The EPICure 2 study. *Archives of Disease in Childhood. Fetal and Neonatal Edition, 99*(3), F181–F188. doi:10.1097/01.ogx.0000456347.54969.f4
Marlow, N., Wolke, D., Bracewell, M. A., & Samara, M. (2005). Neurologic and developmental disability at six years of age after extremely preterm birth. *New England Journal of Medicine, 352*(1), 9–19. doi:10.1056/NEJMoa041367
Marx, V., & Nagy, E. (2015). Fetal behavioural responses to maternal voice and touch. *PLoS One, 10*(6), e0129118. doi:10.1371/journal.pone.0129118
McCain, G. C., Donovan, E. F., & Gartside, P. (1999). Preterm infant behavioral and heart rate responses to antenatal phenobarbital. *Research in Nursing and Health, 22*(6), 461–470. doi:10.1002/(SICI)1098-240X(199912)22:6%3C461::AID-NUR4%3E3.0.CO;2-T
McCain, G. C., Gartside, P. S., Greenberg, J. M., & Lott, J. W. (2001). A feeding protocol for healthy preterm infants that shortens time to oral feeding. *Journal of Pediatrics, 139*(3), 374–379. doi:10.1067/mpd.2001.117077
McMahon, E., Wintermark, P., & Lahav, A. (2012). Auditory brain development in premature infants: The importance of early experience. *Annals of the New York Academy of Sciences, 1252*(1), 17. doi:10.1111/j.1749-6632.2012.06445.x
Meyer, K. A., Wall, M. M., Larson, N. I., Laska, M. N., & Neumark-Sztainer, D. (2012). Sleep duration and BMI in a sample of young adults. *Obesity, 20*(6), 1279–1287. doi:10.1038/oby.2011.381
Michelsson, K., Rinne, A., & Paajanen, S. (1990). Crying, feeding and sleeping patterns in 1 to 12-month-old infants. *Child: Care, Health and Development, 16*(2), 99–111. doi:10.1111/j.1365-2214.1990.tb00642.x
Miller, D. B., & Holditch-Davis, D. (1992). Interactions of parents and nurses with high-risk preterm infants. *Research in Nursing and Health, 15*(3), 187–197. doi:10.1002/nur.4770150305
Milligan, D. W. A. (1979). Cerebral blood flow and sleep state in the normal newborn infant. *Early Human Development, 3*(4), 321–328. doi:10.1016/0378-3782(79)90043-4
Minde, K., Ford, L., Celhoffer, L., & Boukydis, C. (1975). Interactions of mothers and nurses with premature infants. *Canadian Medical Association Journal, 113*(8), 741–745. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1956609
Minde, K., Whitelaw, A., Brown, J., & Fitzhardinge, P. (1983). Effect of neonatal complications in premature infants on early parent-infant

interactions. *Developmental Medicine and Child Neurology, 25*(6), 763–777. doi:10.1111/j.1469-8749.1983.tb13845.x

Mirmiran, M. (1986). The importance of fetal/neonatal REM sleep. *European Journal of Obstetrics, Gynecology, and Reproductive Biology*, *21*(5\6), 283–291. doi:10.1016/0028-2243(86)90006-7

Mirmaran, M., Baldwin, R. B., & Ariagno, R. L. (2003). Circadian and sleep development in preterm infants occurs independently from the influences of environmental lighting. *Pediatric Research, 53*, 933–938. doi:10.1203/01.PDR.0000061541.94620.12

Modesto, I. F., Avelar, A. F., Pedreira, M. da L., Pradella-Hallinan, M., Avena, M. J., & Pinheiro, E. M. (2016). Effect of sleeping position on arousals from sleep in preterm infants. *Journal for the Specialists in Pediatric Nursing, 21*(3), 131–138. doi:10.1111/jspn.12147

Mok, J. Y., Hak, H., McLaughlin, F. J., Pintar, M., Canny, G. J., & Levison, H. (1988). Effect of age and state of wakefulness on transcutaneous oxygen values in preterm infants: A longitudinal study. *Journal of Pediatrics*, *113*(4), 706–709. doi:10.1016/S0022-3476(88)80385-8

Molnar, A., Andréasson, S., Larsson, E., Åkerblom, H., & Holmström, G. (2017). Reduction of rod and cone function in 6.5-year-old children born extremely preterm. *JAMA Ophthalmology, 135*(8), 854–861. doi:10.1001/jamaophthalmol.2017.2069

Moore, D. R., Sieswerda, S. L., Grainger, M. M., Bowling, A., Smith, N., Perdew, A., . . . Hunter, L. L. (2018). Referral and diagnosis of developmental auditory processing disorder in a large, United States hospital-based audiology service. *Journal of the American Academy of Audiology, 29*(5), 364–377. doi:10.3766/jaaa.16130

Moore, K. L., Persaud, T. V. N., & Torchia, M. G. (2015). *The developing human: Clinically oriented embryology* (10th ed.). Philadelphia, PA: Elsevier.

Morsan, V., Fantoni, C., & Tallandini, M. (2018). Age correction in cognitive, linguistic, and motor domains for infants born preterm: An analysis of the Bayley scales of infant and toddler development, third edition developmental patterns. *Developmental Medicine and Child Neurology, 60*(8), 820–825. doi:10.1111/dmcn.13735

Moseley, M. J., Thompson, J. R., Levene, M. I., & Fielder, A. R. (1988). Effects of nursery illumination on frequency of eyelid opening and state in preterm infants. *Early Human Development*, *18*(1), 13–26. doi:10.1016/0378-3782(88)90039-4

Mouradian, L. E., Als, H., & Coster, W. J. (2000). Neurobehavioral functioning of healthy preterm infants of varying gestational ages. *Journal of Developmental and Behavioral Pediatrics, 21*, 408–416. doi:10.1097/00004703-200012000-00002

Mwaniki, M. K., Atieno, M., Lawn, J. E., & Newton, C. R. (2012). Long-term neurodevelopmental outcomes after intrauterine and neonatal insults: A systematic review. *The Lancet, 379*(9814), 445–452. doi:10.1016/S0140-6736(11)61577-8

Myers, B. J., Jarvis, P. A., Creasey, G. L., Kerkering, K. W., Markowitz, P. I., & Best, A. M., III. (1992). Prematurity and respiratory illness: Brazelton Scale (NBAS) performance of preterm infants with bronchopulmonary dysplasia (BPD), respiratory distress syndrome (RDS), or no respiratory illness. *Infant Behavior and Development, 15*(1), 27–42. doi:10.1016/0163-6383(92)90004-P

Neil, J. J., & Inder, T. E. (2018). Neonatal neuroimaging. In C. A. Gleason & S. E. Juul (Eds.), *Avery's diseases of the newborn* (10th ed., pp. 923–951). Philadelphia, PA: Elsevier.

Noble, Y., & Boyd, R. (2012). Neonatal assessment for the preterm infant up to 4 months corrected age: A systematic review. *Developmental Medicine and Child Neurology, 54*, 129–139. doi:10.1111/j.1469-8749.2010.03903.x

Nugent, J. K. (2007). *Understanding newborn behavior and early relationships: The Newborn Behavioral Observations (NBO) system handbook*. Baltimore, MD, US: Paul H Brookes Publishing.

Nugent, J. K., Bartlett, J., Von Ende, A., & Valim, C. (2017). The effects of the newborn behavioral observations (NBO) system on sensitivity in mother–infant interactions. *Infants and Young Children, 30*(4), 257–268. doi:10.1097/IYC.0000000000000103

Nugent, J. K., Lester, B. M., Greene, S. M., Wieczorek-Deering, D., & O'Mahony, P. (1996). The effects of maternal alcohol consumption and cigarette smoking during pregnancy on acoustic cry analysis. *Child Development, 67*(4), 1806–1815. doi:10.2307/1131733

Nunes, M. L., Khan, R. L., Gomes Filho, I., Booij, L., & da Costa, J. C. (2014). Maturational changes of neonatal electroencephalogram: A comparison between intra uterine and extra uterine development. *Clinical Neurophysiology, 125*(6), 1121–1128. doi:10.1016/j.clinph.2013.10.049

Oakes, L. (2017). Plasticity may change inputs as well as processes, structures, and responses. *Cognitive Development, 42*, 4–14. doi:10.1016/j.cogdev.2017.02.012

Obeidat, H., Kahalaf, I., Callister, L. C., & Froelicher, E. S. (2009). Use of facilitated tucking for nonpharmacological pain management in preterm infants: A systematic review. *Journal of Perinatal & Neonatal Nursing, 23*(4), 372–377. doi:10.1097/JPN.0b013e3181bdcf77

O'Brien, C. M., & Jeffery, H. E. (2002). Sleep deprivation, disorganization and fragmentation during opiate withdrawal in newborns. *Journal of Pediatrics and Child Health*, *38*(1), 66–71. doi:10.1046/j.1440-1754.2002.00724.x

Oehler, J. M. (1995). Development of mother-child interaction in very low birth weight infants. In S. G. Funk, E. M. Tornquist, M. T. Champagne, & R. A. Wiese (Eds.), *Key aspects of caring for the acutely ill: Technological aspects, patient education, and quality of life* (pp. 120–133). New York, NY: Springer Publishing Company.

Oehler, J. M., Hannan, T., & Catlett, A. (1993). Maternal views of preterm infants' responsiveness to social interaction. *Neonatal Network, 12*(6), 67–74.

Ohgi, S., Fukuda, M., Moriuchi, H., Kusumoto, T., Akiyama, T., Nugent, J. K., . . . Saitoh, H. (2002). Comparison of kangaroo care and standard care: Behavioral organization, development, and temperament in healthy, low-birth-weight infants through 1 year. *Journal of Perinatology, 22*(5), 374–379. doi:10.1038/sj.jp.7210749

Olischar, M., Klebermass, K., Waldhoer, T., Pollak, A., & Weninger, M. (2007). Background patterns and sleep-wake cycles on amplitude-integrated electroencephalography in preterms younger than 30 weeks gestational age with peri-/intraventricular haemorrhage. *Acta Paediatrica*, *96*(12), 1743–1750. doi:10.1111/j.1651-2227.2007.00462.x

Orsi, K. C., Avena, M. J., Lurdes de Cacia Pradella-Hallinan, M., da Luz Gonçalves Pedreira, M., Tsunemi, M. H., Machado Avelar, A. F., & Pinheiro, E. M. (2017). Effects of handling and environment on preterm newborns sleeping in incubators. *Journal of Obstetric, Gynecologic, and Neonatal Nursing, 46*(2), 238–247. doi:10.1016/j.jogn.2016.09.005

Ottaviano, S., Giannotti, F., Cortesi, F., Bruni, O., & Ottaviano, C. (1996). Sleep characteristics in healthy children from birth to 6 years of age in the urban area of Rome. *Sleep, 19*, 1–3. doi:10.1093/sleep/19.1.1

Palmu, K., Kirjavainen, T., Stjerna, S., Salokivi, T., & Vanhatalo, S. (2013). Sleep wake cycling in early preterm infants: Comparison of polysomnographic recordings with a novel EEG-based index. *Clinical Neurophysiology, 124*(9), 1807–1814. doi:10.1016/j.clinph.2013.03.010

Parmelee, A. H., Jr., & Stern, E. (1972). Development of states in infants. In C. D. Clemente, D. P. Pupura, & E. F. Mayer (Eds.), *Sleep and the maturing nervous system* (pp. 200–215). New York, NY: Academic Press.

Parslow, P. M., Harding, R., Adamson, T. M., & Horne, R. S. (2004). Effects of sleep state and postnatal age on arousal responses induced by mild hypoxia in infants. *Sleep*, *27*(1), 105–109. doi:10.1093/sleep/27.1.105

Patra, K., & Greene, M. (2018). Health care utilization after NICU discharge and neurodevelopmental outcome in the first 2 years of life in preterm infants. *American Journal of Perinatology, 35*(5), 441–447. doi:10.1055/s-0037-1608678

Pavlidis, E., Lloyd, R. O., Mathieson, S., & Boylan, G. B. (2017). A review of important electroencephalogram features for the assessment of brain maturation in premature infants. *Acta Paediatrica, 106*(9), 1394-1408. doi:10.1111/apa.13956

Perez-Roche, T., Altemir, I., Giménez, G., Prieto, E., González, L., López Pisón, J., & Pueyo, P. (2017). Face recognition impairment in small

for gestational age and preterm children. *Research in Developmental Disabilities, 62*, 163–173. doi:10.1016/j.ridd.2017.01.016

Petrou, S., Johnson, S., Wolke, D., & Marlow, N. (2013). The association between neurodevelopmental disability and economic outcomes during mid-childhood. *Child: Care, Health and Development, 39*(3), 345–357. doi:10.1111/j.1365-2214.2012.01368.x

Philben, M. K. (2017). The sound environments and auditory perceptions of the fetus and preterm newborn. In M. Fillippa, P. Kuhn, & W. Westrup (Eds.), *Early vocal contact and preterm infant brain development: Bridging the gaps between research and practice* (pp. 91–112). Cham, Switzerland: Springer.

Phillipson, E. A. (1978). Control of breathing during sleep. *American Review of Respiratory Disease, 118*(5), 909–939. Retrieved from https://www.atsjournals.org/doi/abs/10.1164/arrd.1978.118.5.909

Pickler, R. H., Frankel, H. B., Walsh, K. M., & Thompson, N. M. (1996). Effects of nonnutritive sucking on behavioral organization and feeding performance in preterm infants. *Nursing Research*, *45*, 132–138. Retrieved from https://journals.lww.com/nursingresearchonline/Abstract/1996/05000/Effects_of_Nonnutritive_Sucking_on_Behavioral.2.aspx

Pickler, R. H., Higgins, K. E., & Crummette, B. D. (1993). The effect of nonnutritive sucking on bottle-feeding stress in preterm infants. *Journal of Obstetric, Gynecologic, and Neonatal Nursing*, *22*(3), 230–234. doi:10.1111/j,1552-6909.1993.tb01804.x

Pinato, L., Ribeiro, E. M., Leite, R. F. P., Lopes, T. F., Pessoa, A. L. S., Guissoni Campos, L. M., . . . Giacheti, C. M. (2018). Sleep findings in Brazilian children with congenital Zika syndrome. *Sleep, 41*(3). doi:10.1093/sleep/zsy009

Poduri, A., & Volpe, J. J. (2018a). Neuronal Proliferation. In J. J. Volpe, T. E. Inder, B. T. Darras, L. S. de Vries, A. J. du Plessis, J. J. Neil, & J. M. Perlman (Eds.), *Volpe's neurology of the newborn* (6th ed., pp. 100–119). Philadelphia: Elsevier.

Poduri, A., & Volpe, J. J. (2018b). Neuronal Migration. In J. J. Volpe, T. E. Inder, B. T. Darras, L. S. de Vries, A. J. du Plessis, J. J. Neil, & J. M. Perlman (Eds.), *Volpe's neurology of the newborn* (6th ed., pp. 120–144). Philadelphia: Elsevier.

Prechtl, H. (1974). The behavioural states of the newborn infant (a review). *Brain Research, 76*, 185–212. doi:10.1016/0006-8993(74)90454-5

Prechtl, H. F., & Beintema, J. (1968). *The neurological examination of the full-term newborn infant*. Clinics in Developmental Medicine 63. Suffolk, England: The Lavenham Press.

Prechtl, H. F., Theorell, K., & Blair, A. W. (1973). Behavioural state cycles in abnormal infants. *Developmental Medicine and Child Neurology, 15*(5), 606–615. doi:10.1111/j.1469-8749.1973.tb05171.x

Pressler, J. P., & Hepworth, J. T. (2002). A quantitative use of the NIDCAP® tool. *Clinical Nursing Research*, *11*(1), 89–102. doi:10.1177/105477380201100107

Provasi, J., & Lequien, P. (1993). Effects of nonrigid reclining infant seat on preterm behavioral states and motor activity. *Early Human Development, 35*(2), 129–140. doi:10.1016/0378-3782(93)90098-F

Provenzi, L., Olson, K., Giusti, L., Montirosso, R., DeSantis, A., & Tronick, E. Z. (2018). NICU Network Neurobehavioral Scale: 1-month normative data and variation from birth to 1 month. *Pediatric Research, 83*(6), 1104-1109. doi:10.1038/pr.2018.25

Raju, R., & Radtke, R. (2012). Sleep/wake electroencephalography across the lifespan. *Sleep Medicine Clinics, 7*(1), 13–22. doi:10.1016/j.jsmc.2012.01.001

Ramaekers, V. T., Casaer, P., Daniels, H., Smet, M., & Marchal, G. (1989). The influence of behavioural states on cerebral blood flow velocity patterns in stable preterm infants. *Early Human Development, 20*(3\4), 229–246. doi:10.1016/0378-3782(89)90009-1

Regalado, M. G., Schechtman, V. L., Del Angel, A. P., & Bean, X. D. (1995). Sleep disorganization in cocaine-exposed neonates. *Infant Behavior and Development, 18*(3), 319–327. doi:10.1016/0163-6383(95)90020-9

Richardson, H. L., & Horne, R. S. (2013). Arousal from sleep pathways are affected by the prone sleeping position and preterm birth: Preterm birth, prone sleeping and arousal from sleep. *Early Human Development, 89*(9), 705–711. doi:10.1016/j.earlhumdev.2013.05.001

Rivkees, S. A., Mayes, L., Jacobs, H., & Gross, I. (2004). Rest-activity patterns of premature infants are regulated by cycled lighting. *Pediatrics, 113*(4), 833–839. doi:10.1542/peds.113.4.833

Robinson, J., Moseley, M. J., Thompson, J. R., & Fielder, A. R. (1989). Eyelid opening in preterm neonates. *Archives of Disease in Childhood*, *64*(7, Spec. No.), 943–948. doi:10.1136/adc.64.7_spec_no.943

Roffwarg, H. P., Muzio, J. N., & Dement, W. C. (1966). Ontogenetic development of the human sleep-dream cycle. *Science*, *152*(3722), 604–619. doi:10.1126/science.152.3722.604

Rioualen, S., Roué, J. M., Lefranc, J., Gouillou, M., Nowak, E., Alavi, Z., . . . Sizun, J. (2015). Actigraphy is not a reliable method for measuring sleep patterns in neonates. *Acta Paediatrica, 104*(11), e478–e482. doi:10.1111/apa.13088

Romeo, R., Segaran, J., Leonard, J., Robinson, S., West, M., Mackey, A., . . . Gabrieli, J. (2018). Language exposure relates to structural neural connectivity in childhood. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 38*(36), 7870–7877. doi:10.1523/JNEUROSCI.0484-18.2018

Rose, T., & Bonhoeffer, T. (2018). Experience-dependent plasticity in the lateral geniculate nucleus. *Current Opinion in Neurobiology, 53*, 22–28. doi:10.1016/j.conb.2018.04.016

Rosenthal, M. K. (1983). State variations in the newborn and mother-infant interaction during breast feeding: Some sex differences. *Developmental Psychology*, *19*(5), 740–745. doi:10.1037/0012-1649.19.5.740

Ross, K. R., & Rosen, C. L. (2014). Sleep and respiratory physiology in children. *Clinical Chest Medicine, 35*(3), 457–467. doi:10.1016/j.ccm.2014.06.003

Sadeh, A., Dark, I., & Vohr, B. R. (1996). Newborns' sleep-wake patterns: The role of maternal, delivery and infant factors. *Early Human Development, 44*(2), 113–126. doi:10.1016/0378-3782(95)01698-8

Sahni, R., Schulze, K. F., Stefanski, M., Myers, M. M., & Fifer, W. P. (1995). Methodological issues in coding sleep states in immature infants. *Developmental Psychobiology*, *28*(2), 85–101. doi:10.1002/dev.420280203

Saiki, T., Rao, H., Landolfo, F., Smith, A. P., Hannam, S., Rafferty, G. F., & Greenough, A. (2009). Sleeping position, oxygenation and lung function in prematurely born infants studied post term. *Archives of Disease in Childhood: Fetal and Neonatal Edition, 94*(2), F133–F137. doi:10.1136/adc.2008.141374

Samuelsson, M., Holsti, A., Adamsson, M., Serenius, F., Hägglöf, B., & Farooqi, A. (2017). Behavioral patterns in adolescents born at 23 to 25 weeks of gestation. *Pediatrics, 140*(1), e20170199. doi:10.1542/peds.2017-0199

Sarnat, H., Flores-Sarnat, L., & Wei, X. (2017). Olfactory development, part 1: Function, from fetal perception to adult wine-tasting. *Journal of Child Neurology, 32*(6), 566–578. doi:10.1177/0883073817690867

Scafidi, F. A., Field, T. M., Schanberg, S. M., Bauer, C. R., Tucci, K., Roberts, J., . . . Kuhn, C. M. (1990). Massage stimulates growth in preterm infants: A replication. *Infant Behavior and Development*, *13*(2), 167–168. doi:10.1016/0163-6383(90)90029-8

Scher, A. (1991). A longitudinal study of night waking in the first year. *Child: Care, Health and Development, 17*(5), 295–302. doi:10.1111/j.1365-2214.1991.tb00699.x

Scher, M. S., Johnson, M. W., & Holditch-Davis, D. (2005). Cyclicity of neonatal sleep behaviors at 25 to 30 weeks' postconceptional age. *Pediatric Research*, *57*(6), 879–882. doi:10.1203/01.PDR.0000157678.84132.A8

Scher, M. S., Johnson, M. W., Ludington, S. M., & Loparo, K. (2011). Physiologic brain dysmaturity in late preterm infants. *Pediatric Research*, *70*(5), 524–528. doi:10.1203/PDR.0b013e31822f24af

Scher, M. S., Ludington-Hoe, S., Kaffashi, F., Johnson, M. W., Holditch-Davis, D., & Loparo, K. A. (2009). Neurophysiologic assessment of brain maturation after an 8 weeks trial of skin-to-skin contact on preterm infants. *Clinical Neurophysiology*, *120*(10), 1812–1818. doi:10.1016/j.clinph.2009.08.004

Scher, M. S., Richardson, G. A., Coble, P. A., Day, N. L., & Stoffer, D. S. (1988). The effects of prenatal alcohol and marijuana exposure:

Disturbances in neonatal sleep cycling and arousal. *Pediatric Research, 24*(1), 101–105. doi:10.1203/00006450-198807000-00023

Scher, M. S., Sun, M., Steppe, D. A., Guthrie, R. D., & Sclabassi, R. J. (1994). Comparisons of EEG spectral and correlation measures between healthy term and preterm infants. *Pediatric Neurology, 10*(2), 104–108. doi:10.1016/0887-8994(94)90041-8

Schulte, F. J., Busse, C., & Eichhorn, W. (1977). Rapid eye movement sleep, motoneuron inhibition, and apneic spells in preterm infants. *Pediatric Research*, *11*(6), 709–713. doi:10.1203/00006450-197706000-00002

Schwartz, R., Moody, L., Yarandi, H., & Anderson, G. C. (1987). A meta-analysis of critical outcome variables in nonnutritive sucking in preterm infants. *Nursing Research, 36*(5), 292–295. doi:10.1097/00006199-198709000-00010

Schwichtenberg, A. J., Anders, T. F., Vollbrecht, M., & Poehlmann, J. (2011). Daytime sleep and parenting interactions in infants born preterm. *Journal of Developmental and Behavioral Pediatrics, 32*(1), 8–17. doi:10.1097/DBP.0b013e3181fa57e4

Schwichtenberg, A. J., & Poehlmann, J. (2009). A transactional model of sleep-wake regulation in infants born preterm or low birthweight. *Journal of Pediatric Psychology, 34*(8), 837–849. doi:10.1093/jpepsy/jsn132

Schwichtenberg, A. J., Shah, P. E., & Poehlmann, J. (2013). Sleep and attachment in preterm infants. *Infant Mental Health Journal, 34*(1), 37–46. doi:10.1002/imhj.21374

Schwindt, E., Thaller, C., Czaba-Hnizdo, C., Giordano, V., Olischar, M., Waldhoer, T., . . . Klebermass-Schrehof, K. (2015). Being born small for gestational age influences amplitude-integrated electroencephalography and later outcome in preterm infants. *Neonatology, 108*(2), 81–87. doi:10.1159/000382013

Sevestre, A., Oger, E., Bertelle, V., Mabin, D., & Sizun, J. (2013). Agreement between behavioural observation and polygraphs for the diagnosis of sleep-wake states in preterm neonates. *Acta Paediatrica, 102*(5), e229–e231. doi:10.1111/apa.12185

Shaywitz, B. A., Finkelstein, J., Hellman, L., & Weitzman, E. D. (1971). Growth hormone in newborn infants during sleep–wake periods. *Pediatrics, 48*(1), 103–109. Retrieved from https://pediatrics.aappublications.org/content/48/1/103

Shellhaas, R. A., Burns, J. W., Barks, J. D., & Chervin, R. D. (2014). Quantitative sleep stage analyses as a window to neonatal neurologic function. *Neurology, 82*(5), 390–395. doi:10.1212/WNL.0000000000000085

Shimada, M., Takahashi, K., Segawa, M., Higurashi, M., Samejim, M., & Horiuchi, K. (1999). Emerging and entraining patterns of the sleep-wake rhythm in preterm and term infants. *Brain & Development, 21*, 468–473. doi:10.1016/S0387-7604(99)00054-6

Simakajornboon, N., Beckerman, R. C., Mack, C., Sharon, D., & Gozal, D. (2002). Effect of supplemental oxygen on sleep architecture and cardiorespiratory events in preterm infants. *Pediatrics*, *110*(5), 884–888. doi:10.1542/peds.110.5.884

Smith, A. P., Saiki, T., Hannam, S., Rafferty, G. F., & Greenough, A. (2010). The effects of sleeping position on ventilatory responses to carbon dioxide in premature infants. *Thorax, 65*(9), 824–828. doi:10.1136/thx.2009.127837

Snider, L., Tremblay, S., Limperopoulos, C., Majnemer, A., Filion, F., & Johnston, C. (2005). Construct validity of the neurobehavioral assessment of preterm infants. *Physical and Occupational Therapy in Pediatrics, 25*(3), 81–95. doi:10.1080/J006v25n03_06

Snyder, R., Herdt, A., Mejias-Cepeda, N., Ladino, J., Crowley, K., & Levy, P. (2017). Early provision of oropharyngeal colostrum leads to sustained breast milk feedings in preterm infants. *Pediatrics & Neonatology, 58*(6), 534–540. doi:10.1016/j.pedneo.2017.04.003

Sommers, R., Tucker, R., & Laptook, A. (2011). Amplitude-integrated EEG differences in premature infants with and without bronchopulmonary dysplasia: A cross-sectional study. *Acta Paediatrica, 100*(11), 1437–1441. doi:10.1111/j.1651-2227.2011.02393.x

Soubasi, V., Mitsakis, K., Nakas, C. T., Petridou, S., Sarafidis, K., Griva, M., . . . Drossou, V. (2009). The influence of extrauterine life on the aEEG maturation in normal preterm infants. *Early Human Development*, *85*(12), 761–765. doi:10.1016/j.earlhumdev.2009.10.004

Spittle, A. T., K. (2016). The role of early developmental intervention to influence neurobehavioral outcomes of children born preterm. *Seminars in Perinatology, 40*(8), 542–548. doi:10.1053/j.semperi.2016.09.006

St. James-Roberts, I., & Plewis, I. (1996). Individual differences, daily fluctuations, and developmental changes in amounts of infant waking, fussing, crying, and sleeping. *Child Development*, *67*(5), 2527–2540. doi:10.2307/1131638

Stéphan-Blanchard, E., Chardon, K., Léké, A., Delanaud, S., Djeddi, D., Libert, J. P., . . . Telliez, F. (2010). In utero exposure to smoking and peripheral chemoreceptor function in preterm neonates. *Pediatrics, 125*(3), e592–e599. doi:10.1542/peds.2008-2976

Stéphan-Blanchard, E., Telliez, F., Léké, A., Djeddi, D., Bach, V., Libert, J. P., & Chardon, K. (2008). In utero exposure to smoking and peripheral chemoreceptor function in preterm neonates. *Sleep, 31*(12), 1683–1689. doi:10.1093/sleep/31.12.1683

Stevens, B. J., Johnston, C. C., & Horton, L. (1994). Factors that influence the behavioral pain responses of premature infants. *Pain, 59*, 101–109. doi:10.1016/0304-3959(94)90053-1

Stokes, A., Agthe, A. G., & El Metwally, D. (2018). Music exposure and maturation of late preterm sleep-wake cycles: A randomised crossover trial. *Acta Paediatrica, 107*(4), 582–586. doi:10.1111/apa.14079

Sullivan, C. E. (1980). Breathing in sleep. In J. Orem & C. D. Barnes (Eds.), *Physiology in sleep* (pp. 213–272). New York, NY: Academic Press.

Sullivan, M. C., Msall, M. E., & Miller, R. J. (2012). 17-year outcome of preterm infants with diverse neonatal morbidities: Part 1-Impact on physical, neurological, and psychological health status. *Journal for Specialists in Pediatric Nursing*, *17*(3), 226–241. doi:10.1111/j.1744-6155.2012.00337.x

Symanski, M. E., Hayes, M. J., & Akilesh, M. K. (2002). Patterns of premature newborns' sleep-wake states before and after nursing interventions on the night shift. *Journal of Obstetric, Gynecologic, and Neonatal Nursing, 31*(3), 305–313. doi:10.1111/j.1552-6909.2002.tb00052.x

Symes, A. (2016). Developmental outcomes. In M. G. MacDonald & M. M. Seshia (Eds.), *Avery's neonatology: Pathophysiology & management of the newborn* (7th ed., pp. 1157–1168). Philadelphia, PA: Wolters Kluwer.

Synnes, A., & Hicks, M. (2018). Neurodevelopmental outcomes of preterm children at school age and beyond. *Clinics in Perinatology, 45*(3), 393–408. doi:10.1016/j.clp.2018.05.002

Thiriez, G., Mougey, C., Vermeylen, D., Wermenbol, V., Lanquart, J. P., Lin, J. S., & Franco, P. (2015). Altered autonomic control in preterm newborns with impaired neurological outcomes. *Clinical Autonomic Research, 25*(4), 233–242. doi:10.1007/s10286-015-0298-6

Thoman, E. B. (1975). Early development of sleeping behaviors in infants. In N. R. Ellis (Ed.), *Aberrant development in infancy: Human and animal studies* (pp. 122–138). New York, NY: John Wiley & Sons.

Thoman, E. B. (1990). Sleeping and waking states in infants: A functional perspective. *Neuroscience and Biobehavioral Reviews*, *14*(1), 93–107. doi:10.1016/s0149-7634(05)80165-4

Thoman, E. B., Acebo, C., & Becker, P. T. (1983). Infant crying and stability in the mother-infant relationship: A systems analysis. *Child Development, 54*(3), 653–659. doi:10.2307/1130052

Thoman, E. B., Denenberg, V. H., Sieval, J., Zeider, L. P., & Becker, P. (1981). State organization in neonates: Developmental inconsistency indicates risk for developmental dysfunction. *Neuropediatrics, 12*(1), 45–54. doi:10.1055/s-2008-1059638

Thoman, E. B., & Glazier, R. R. (1987). Computer scoring of motility patterns for states of sleep and wakefulness: Human infants. *Sleep, 10*(2), 122–129. doi:10.1093/sleep/10.2.122

Thoman, E. B., & Graham, S. E. (1986). Self-regulation of stimulation by premature infants. *Pediatrics, 78*(5), 855–860. Retrieved from https://pediatrics.aappublications.org/content/78/5/855

Thoman, E. B., Holditch Davis, D., & Denenberg, V. H. (1987). The sleeping and waking states of infants: Correlations across

time and person. *Physiology and Behavior, 41*(6), 531–537. doi:10.1016/0031-9384(87)90307-6

Thoman, E. B., Holditch-Davis, D., Graham, S. E., Scholz, J. P., & Rowe, J. C. (1988). Infants at risk for sudden infant death syndrome (SIDS): Differential prediction for three siblings of SIDS infants. *Journal of Behavioral Medicine, 11*(6), 565–583. doi:10.1007/bf00844906

Thoman, E. B., Holditch-Davis, D., Raye, J. R., Philipps, A. F., Rowe, J. C., & Denenberg, V. H. (1985). Theophylline affects sleep-wake state development in premature infants. *Neuropediatrics, 16*(1), 13–18. doi:10.1055/s-2008-1052537

Thoman, E. B., Ingersoll, E. W., & Acebo, C. (1991). Premature infants seek rhythmic stimulation, and the experience facilitates neurobehavioral development. *Journal of Behavioral and Developmental Pediatrics*, *12*(1), 11–18. doi:10.1097/00004703-199102000-00004

Thoman, E. B., & Whitney, M. P. (1989). Sleep states of infants monitored in the home: Individual differences, developmental trends, and origins of diurnal cyclicity. *Infant Behavior and Development, 12*(1), 59–75. doi:10.1016/0163-6383(89)90053-2

Thomas, K. A. (2000). Differential effects of breast- and formula-feeding on preterms' sleep-wake patterns. *Journal of Obstetric, Gynecologic and Neonatal Nursing, 29*(2), 145–152. doi:10.1111/j.1552-6909.2000.tb02034.x

Thomas, K. A., & Foreman, S. W. (2005). Infant sleep and feeding pattern: Effects on maternal sleep. *Journal of Midwifery and Women's Health, 50*(5), 399–404. doi:10.1016/j.jmwh.2005.04.010

Tikotzky, L., De Marcas, G., Har-Toov, J., Dollberg, S., Bar-Haim, Y., & Sadeh, A. (2010). Sleep and physical growth in infants during the first 6 months. *Journal of Sleep Research*, *19*(1 Pt. 1), 103–110. doi:10.1111/j.1365-2869.2009.00772.x

Tilmanne, J., Urbain, J., Kothare, M. V., Wouwer, A. V., & Kothare, S. V. (2009). Algorithms for sleep-wake identification using actigraphy: A comparative study and new results. *Journal of Sleep Research, 18*(1), 85–98. doi:10.1111/j.1365-2869.2008.00706.x

Topcuoglu, S., Kolsuz, L. D., Gursoy, T., Ovali, F., & Karatekin, G. (2016). Effects of preeclampsia on the amplitude integrated electroencephalography activity in preterm infants. *Journal of Perinatal Medicine, 44*(3), 345–349. doi:10.1515/jpm-2015-0096

Torres, C., Holditch-Davis, D., O'Hale, A., & D'Auria, J. (1997). Effect of standardized rest periods on apnea and weight gain of convalescent preterm infants. *Neonatal Network, 16*(8), 35–43.

Tourneux, P., Léké, A., Kongolo, G., Cardot, V., Dégrugilliers, L., Chardon, K., . . . Bach, V. (2008). Relationship between functional residual capacity and oxygen desaturation during short central apneic events during sleep in "late preterm" infants. *Pediatric Research, 64*(2), 171–176. doi:10.1203/pdr.0b013e318179951d

Van Cleve, L., Johnson, L., Andrews, S., Hawkins, S., & Newbold, J. (1995). Pain responses of hospitalized neonates to venipuncture. *Neonatal Network*, *14*(6), 31–36.

Van Ravenswaaij-Arts, C. M. A., Hopman, J. C. W., & Kollee, L. A. A. (1989). *Influence of Behavioural State on Blood Pressure in Preterm Infants during the First 5 Days of Life. Acta Pediatrica, 78*(3) 358–363. doi:10.1111/j.1651-2227.1989.tb11092.x

Varvara, B., Effrossine, T., Despoina, K., Konstantinos, D., & Matziou, V. (2016). Effects of neonatal intensive care unit nursing conditions in neonatal NREM sleep. *Journal of Neonatal Nursing, 22*(3), 115–125. doi:10.1016/j.jnn.2015.11.004

Vecchierini, M.-F., Curzi-Dascolova, L., Ha, T.-P., Bloch, J., & Gaultier, C. (2001). Patterns of EEG frequency, movement, heart rate, and oxygenation after isolated short apneas in infants. *Pediatric Research, 49*, 220–226. doi:10.1203/00006450-200102000-00015

Vesoulis, Z. A., Paul, R. A., Mitchell, T. J., Wong, C., Inder, T. E., & Mathur, A. M. (2015). Normative amplitude-integrated EEG measures in preterm infants. *Journal of Perinatology, 35*(6), 428–443. doi:10.1038/jp.2014.225

Vohr, B. R., Karp, D., O'Dea, C., Darrow, D., Coll, C. G., Lester, B. M., . . . Cashore, W. (1990). Behavioral changes correlated with brain-stem auditory evoked responses in term infants with moderate hyperbilirubinemia. *Journal of Pediatrics, 117*(2 Pt. 1), 288–291. doi:10.1016/S0022-3476(05)80549-9

Volpe, J. J. (2018). Neurological examination: Normal and abnormal features. In J. J. Volpe, T. E. Inder, B. T. Darras, L. S. de Vries, A. J. du Plessis, J. J. Neil, & J. M. Perlman (Eds.), *Volpe's neurology of the newborn* (6th ed., pp. 191–221). Philadelphia, PA: Elsevier.

Wang, K., Difiore, J. M., Martin, R. J., Rosen, C. L., & Hibbs, A. M. (2013). Markers for severity of illness associated with decreased snoring in toddlers born ELGA. *Acta Paediatrica, 102*(1), e39–e43. doi:10.1111/apa.12033

Watt, J. E., & Strongman, K. T. (1985). The organization and stability of sleep states in full-term, preterm, and small-for-gestational-age infants: A comparative study. *Developmental Psychobiology, 18*(2), 151–162. doi:10.1002/dev.420180207

Weissbluth, M. (1995). Naps in children: 6 months-7 years. *Sleep*, *18*(2), 82–87. doi:10.1093/sleep/18.2.82

Weisman, O., Aderka, I. M., Marom, S., Hermesh, H., & Gilboa-Schechtman, E. (2011). Sleep-wake transitions in premature neonates predict early development. *Pediatrics, 128*(4), 706–714. doi:10.1542/peds.2011-0047

Welch, M. G., Myers, M. M., Grieve, P. G., Isler, J. R., Fifer, W. P., Sahni R, . . . Sopteriam, S. (2014). Electroencephalographic activity of preterm infants is increased by family nurture intervention: A randomized controlled trial in the NICU. *Clinical Neurophysiology, 125*(4), 675–684. doi:10.1016/j.clinph.2013.08.021

Welch, M. G., Stark, R. I., Grieve, P. G., Ludwig, R. J., Isler, J. R., Barone, J. L., & Myers, M. M. (2017). Family nurture intervention in preterm infants increases early development of cortical activity and independence of regional power trajectories. *Acta Paediatrica, 106*(12), 1952–1960. doi:10.1111/apa.14050

Werchan, D., Baumgartner, H., Lewkowicz, D., & Amso, D. (2018). The origins of cortical multisensory dynamics: Evidence from human infants. *Developmental Cognitive Neuroscience, 34*, 75–81. doi:10.1016/j.dcn.2018.07.002

Werth, J., Atallah, L., Andriessen, P., Long, X., Zwartkruis-Pelgrim, E., & Aarts, R. M. (2017). Unobtrusive sleep state measurements in preterm infants - A review. *Sleep Medicine Reviews, 32*, 109–122. doi:10.1016/j.smrv.2016.03.005

Werth, J., Long, X., Zwartkruis-Pelgrim, E., Niemarkt, H., Chen, W., Aarts, R. M., & Andriessen, P. (2017). Unobtrusive assessment of neonatal sleep state based on heart rate variability retrieved from electrocardiography used for regular patient monitoring. *Early Human Development, 113*, 104–113. doi:10.1016/j.earlhumdev.2017.07.004

Westrup, B., Hellström-Westas, L., Stjernqvist, K., & Lagercrantz, H. (2002). No indication of increased quiet sleep in infants receiving care based on the newborn individualized developmental care and assessment program (NIDCAP). *Acta Paediatrica, 91*(3), 318–322. doi:10.1111/j.1651-2227.2002.tb01722.x

White-Traut, R. C., Berbaum, M. L., Lessen, B., McFarlin, B., & Cardenas, L. (2005). Feeding readiness in preterm infants: The relationship between preterm behavioral state and feeding readiness behaviors and efficiency during transition from gavage to oral feeding. *American Journal of Maternal Child Nursing*, *30*(1), 52–59. Retrieved from https://journals.lww.com/mcnjournal/Abstract/2005/01000/Feeding_Readiness_in_Preterm_Infants__The.14.aspx

White-Traut, R. C., Nelson, M. N., Silvestri, J. M., Cunningham, N., & Patel, M. (1997). Response of preterm infants to unimodal and multimodal sensory intervention. *Pediatric Nursing*, *23*, 169–175, 193.

White-Traut, R. C., Nelson, M. N., Silvestri, J. M., Patel, M. K., & Kilgallon, D. (1993). Patterns of physiologic and behavioral response of intermediate care preterm infants to intervention. *Pediatric Nursing*, 19(6), 625–629.

White-Traut, R. C., Nelson, M. N., Silvestri, J. M., Patel, M., Vasan, U., Han, B. K., . . . Bradford, L. (1999). Developmental intervention for preterm infants diagnosed with periventricular leukomalacia. *Research in Nursing and Health, 22*(2), 131–143. doi:10.1002/(sici)1098-240x(199904)22:2%3C131::aid-nur5%3E3.0.co;2-e

White-Traut, R. C., & Pate, C. M. (1987). Modulating infant state in premature infants. *Journal of Pediatric Nursing, 2*(2), 96–101.

White-Traut, R. C., Studer, T., Meleedy-Rey, P., Murray, P., Labovsky, S., & Kahn, J. (2002). Pulse rate and behavioral state correlates after auditory, tactile, visual, and vestibular intervention in drug-exposed

neonates. *Journal of Perinatology, 22*(4), 291–299. doi:10.1038/sj.jp.7210695

Whitehead, K., Laudiano-Dray, M., Meek, J., & Fabrizi, L. (2018). Emergence of mature cortical activity in wakefulness and sleep in healthy preterm and full-term infants. *Sleep, 41*(8). doi:10.1093/sleep/zsy096

Whitney, M. P., & Thoman, E. B. (1993). Early sleep patterns of premature infants are differentially related to later developmental disabilities. *Journal of Developmental and Behavioral Pediatrics, 14*(2), 71–80. doi:10.1097/00004703-199304000-00001

Whitney, M. P., & Thoman, E. B. (1994). Sleep in premature and full term infants from 24-hours home recordings. *Infant Behavior and Development, 17*(3), 223–234. doi:10.1016/0163-6383(94)90001-9

Wikström, S., Pupp, I. H., Rosén, I., Norman, E., Fellman, V., Ley, D., & Hellström-Westas, L. (2012). Early single-channel aEEG/EEG predicts outcome in very preterm infants. *Acta Paediatrica, 101*(7), 719–726. doi:10.1111/j.1651-2227.2012.02677.x

Winkler, M. R., Park, J., Pan, W., Brandon, D. H., Scher, M., & Holditch-Davis, D. (2017). Does preterm period sleep development predict early childhood growth trajectories? *Journal of Perinatology,* 37(9), 1047–1052. doi:10.1038/jp.2017.91

Witcombe, N. B., Yiallourou, S. R., Walker, A. M., & Horne, R. S. (2008). Blood pressure and heart rate patterns during sleep are altered in preterm-born infants: Implications for sudden infant death syndrome. *Pediatrics*, *122*(6), e1242–e1248. doi:10.1542/peds.2008-1400

Wolff, P. H. (1959). Observations on newborn infants. *Psychosomatic Medicine, 21*(2), 110–118. doi:10.1097/00006842-195903000-00004

Wolff, P. H. (1966). The causes, controls, and organization of behavior in the neonate. *Psychological Issues*, *5*(1), 1–105.

Wolke, D., Söhne, B., Riegel, K., Ohrt, B., & Osterlund, K. (1998). An epidemiologic longitudinal study of sleeping problems and feeding experience of preterm and term children in southern Finland: Comparison with a southern German population sample. *Journal of Pediatrics*, *133*(2), 224–231. doi:10.1016/s0022-3476(98)70224-0

Wong, F. Y., Witcombe, N. B., Yiallourou, S. R., Yorkston, S., Dymowski, A. R., Krishnan, L., . . . Horne, R. S. (2011). Cerebral oxygenation is depressed during sleep in healthy term infants when they sleep prone. *Pediatrics, 127*(3), e558–e565. doi:10.1542/peds.2010-2724

Woods, N. S., Eyler, F. D., Behnke, M., & Conlon, M. (1993). Cocaine use during pregnancy: Maternal depressive symptoms and infant neurobehavior over the first month. *Infant Behavior and Development, 16*(1), 83–98. doi:10.1016/0163-6383(93)80030-c

Woodson, R., Field, T., & Greenberg, R. (1983). Estimating neonatal oxygen consumption from heart rate. *Psychophysiology, 20*(5), 558–561. doi:10.1111/j.1469-8986.1983.tb03013.x

Yiallourou, S. R., Witcombe, N. B., Sands, S. A., Walker, A. M., & Horne, RS. (2013). The development of autonomic cardiovascular control is altered by preterm birth. *Early Human Development, 89*(3), 145–152. doi:10.1016/j.earlhumdev.2012.09.009

Yildiz, A., Arikan, D., Gozum, S., Tastekin, A., & Budancamanak, I. (2011). The effect of the odor of breast milk on the time needed for transition from gavage to total oral feeding in preterm infants. *Journal of Nursing Scholarship, 43*(3), 265–273. doi:10.1111/j.1547-5069.2011.01410.x

Younge, N., Goldstein, R. F., Bann, C. M., Hintz, S. R., Patel, R. M., Smith, P. B., . . . Cotten, C. M. (2017). Survival and neurodevelopmental outcomes among periviable infants. *New England Journal of Medicine, 376*(7), 617–628. doi:10.1056/NEJMoa1605566

Yuskaitis, C. J., & Pomeroy, S. L. (2017). Development of the nervous system. In R. A. Polin, S. H. Abman, D. H. Rowitch, W. E. Benitz, & Fox, W. W. (Eds.), *Fetal and neonatal physiology* (5th ed., Vol. 2, pp. 1294–1313). Philadelphia, PA: Elsevier.

Zahr, L. K., & Balian, S. (1995). Responses of premature infants to routine nursing interventions and noise in the NICU. *Nursing Research, 44*(3), 179–185. doi:10.1097/00006199-199505000-00009

Zhang, S., Su, F., Li, J., & Chen, W. (2018). The analgesic effects of maternal milk odor on newborns: A meta-analysis. *Breastfeeding Medicine: The Official Journal of the Academy of Breastfeeding Medicine, 13*(5), 327–334. doi:10.1089/bfm.2017.0226

Zimmerman, E., & DeSousa, C. (2018). Social visual stimuli increase infants suck response: A preliminary study. *PLoS One, 13*(11), e0207230. doi: 10.1371/journal.pone.0207230

Zores, C., Dufour, A., Pebayle, T., Dahan, I., Astruc, D., & Kuhn, P. (2018). Observational study found that even small variations in light can wake up very preterm infants in a neonatal intensive care unit. *Acta Paediatrica, 107*(7), 1191–1197. doi:10.1111/apa.14261

Zubiaurre-Elorza, L., Linke, A. C., Herzmann, C., Wild, C. J., Duffy, H., Lee, D., . . . Cusack, R. (2018). Auditory structural connectivity in preterm and healthy term infants during the first postnatal year. *Developmental Psychobiology, 60*(3), 256–264. doi:10.1002/dev.21610

CHAPTER 32

The Neonatal Intensive Care Unit (NICU) Environment

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INTRAUTERINE VERSUS EXTRAUTERINE ENVIRONMENTS

It is well known that premature infants experience multiple physical and developmental challenges related in varying degrees to the fact that their "fetal" development occurs outside the womb in the extrauterine environment of the NICU. To better understand the correlation of early environmental factors to the developmental problems associated with prematurity, it is essential to examine (and often modify) the environment in which these infants spend a critical period of their development. This chapter highlights differences in the intrauterine environment (maternal womb) compared with the extrauterine environment (NICU); the effects these differences have on fetal/infant neurosensory and neurobehavioral development; and what can be done to optimize the NICU environment to provide a healing, nurturing place for premature infants to grow, mature, and form secure bonds of attachments with their families.

From the first moments of life, the premature infant is abruptly separated from the dimly lit, temperature-controlled, fluid-filled womb of the mother in which it has been growing and is suddenly exposed to a significantly cooler environment that often contains noxious smells and tastes, loud sounds, bright lights, and a multitude of painful procedures along with repetitive, non-nurturing handling. These altered sensory experiences can have a negative impact on an infant's brain and emotional development. The mismatch between the NICU environment and the preterm infant's developing brain and neurologic system increases the risk for poor developmental outcomes, including emotional, cognitive, motor, and sensory abnormalities (Gorzilio, Garrido, Gaspardo, Martinez, & Linhares, 2015).

The full-term healthy infant, more often than not, has a consistent nurturing caregiver as well as an appropriate variety of stimulations. The full-term infant with 40 weeks of intrauterine development is ready for a variety of sensory experiences, including tactile, gustatory, olfactory, auditory, and visual experiences. Appropriate patterns of adaptation, cognitive learning, and motor control are formed when sensory information interacts in developmentally appropriate ways with experience. On the other hand, a premature infant typically is exposed to numerous caregivers and high levels of inappropriate sensory input that can alter adaptation patterns.

The neurologic and sensory systems do not exist as separate entities but are interdependent and comprise the neurobehavioral and neurosensory development of the infant. Every sensory experience is recorded in the brain, leading to a behavioral response, thereby leading to yet another sensory experience. The human brain comprises 86 billion neurons and an even more staggering number of synapses, dendrites, axons, and glia cells connecting and supporting them, with the vast majority of these cells formed during prenatal development. After birth, the "fetal" brain continues making synaptic connections at a rate of 40,000 connections per minute and must continue critical neurologic growth and maturation in the often harsh extrauterine NICU environment (Azevedo et al., 2009; Keunen, Counsell, & Benders, 2017). While axons continue to grow, facilitating major connections in the white matter to find their cortical targets, the overlying cortex transforms its relatively smooth surface into a highly convoluted mantle with secondary and tertiary sulci that resembles the adult human brain (Striedter, Srinivasan, & Monuki, 2014). MRI studies in preterm infants have reported a fivefold increase in cortical surface area and doubling of cortical curvature measures in the time frame that coincides with the third trimester of pregnancy (Moeskops et al., 2015).

Brain development in the fetus, neonate, and infant includes not just sensory systems but motor systems, social/emotional systems, and the cognitive system, which are connected and integrated during development. The maternal womb, or intrauterine environment, is conducive to positive sensory input, which is crucial for normal brain development in a developing fetus. The intrauterine environment protects the developing fetus against harsh outside stimulation while providing a variety of tactile, vestibular, chemical, visual, and auditory sensory stimuli in an integrated, multimodal fashion (Lickliter, 2011). The intrauterine environment of a developing fetus is characterized by generalized extremity flexion and containment, limited light and noise exposure, sleep cycle preservation, and unrestricted access to the mother via somatosensory, auditory, and chemosensory pathways. The uterine wall provides secure boundaries for the developing fetus. Vestibular and tactile stimuli come from maternal and fetal movements and from contact with warm amniotic fluid as well as from contact with body parts and the wall of the uterus. Hormonal cycles of the mother provide rhythmic and cyclical stimulation. Nutritional needs of the fetus are met by the placenta. Auditory input includes maternal voice, bowel sounds, blood flow through the placenta

and umbilical cord, and filtered sounds from the extrauterine environment, transmitted through liquid and solid media.

Prematurely born neonates in the NICU are exposed to fluctuations in temperature, touch, light, sound, olfaction, oxygen, and nutrients that are very different from those they have experienced in utero. These negative sensory inputs replace the positive sensory inputs in the developing brain, which can permanently alter normal brain development. The architecture of connections in the brain is made with dendritic growth, synaptic networks, apoptosis, myelination, and pruning. Research shows that outside stimulation from the environment can induce changes in the pattern of brain development designed to occur in the last trimester of pregnancy and in early life, altering the development and impacting the quality of these connections (Keunen et al., 2017).

MRI performed on brains of infants born 10 weeks prematurely showed 30% less gray matter (the brain's thinking cells) and 40% less white matter (connections in the brain; A. Dunn, 2003; Keunen et al., 2017). Hebbian Associative Learning was derived by Donald Hebb in 1949 and includes what is now known as Hebb's law. While Hebb's law states that "neurons that fire together, wire together," it implies that "neurons that don't, won't," or that "neurons that fire apart, wire apart." This means that repeated experiences (positive or negative) reinforce particular patterns of synaptic connections (wiring) and a lack of appropriate experiences diminishes the firing of neurons, impacting the ability to "hardwire" synapses, thus altering the developing brain (Hebb, 1949).

When an infant is born prematurely, the still-developing brain and sensory systems are affected by the continuous interplay of stimuli in the NICU. Events, stimuli, and environmental factors can support the processes of sensory development or create significant interference. Sensory interference may occur when immature sensory systems are stimulated out of turn or with inappropriate stimuli. It is essential that background neurosensory stimulation be kept at a level such that sensory systems can discriminate and accommodate meaningful signals or stimulation. This observation is especially true for sound, touch, smell, position, and comfort, which are part of early neurosensory development and in utero learning (or NICU learning; Graven, 2006).

Because the developing brain is extremely sensitive to the appropriate levels of sensory stimuli, alterations can result in abnormal structural and functional development of the brain and could account for the behavioral, cognitive, and functional deficits that many premature infants manifest (Keunen et al., 2017; Rees, Harding, & Walker, 2011). Babies of low birth weight, or very low birth weight (VLBW), many of whom are also small for gestational age, are at increased risk for auditory and visual impairment including sensorineural hearing loss and deficits in visual acuity, color vision, and contrast sensitivity. Additionally, long-term alterations in retinal function and subtle deficits in neural conduction in auditory pathways have all been demonstrated (Bouyssi-Kobar et al., 2018).

It is well documented that prematurely born infants have a high risk of developmental and behavioral disorders compared with those born at term (Hutchon, 2018; Leversen et al., 2011; Saigal & Doyle, 2008). Because sensory experience is the basis for much of learning in infancy, sensory problems that affect preterm infants may contribute to their high incidence of later developmental disorders (Chorna, Solomon, Slaughter, Stark, & Maitre, 2014). Hearing and visual impairment, language delays, and sensory processing issues may also occur because fetal sensory development has been interrupted by preterm birth and exposed to the unpredictable sensory input of the NICU (Malcolm, 2015; Papageorgiou & Pelausa, 2014). Although hearing and vision impairments are well-known sensory outcomes of prematurity, abnormalities in sensory processing, the organization of sensation for use, and sensory reactivity, an observable and immediate modulation of behavior in response to a sensory stimulus, are more difficult to identify and characterize (Papageorgiou & Pelausa, 2014).

Even the full-term neonate's neurologic system is in a highly active stage of development at birth. With volumes of research demonstrating long-term disabilities in preterm-born children, understanding how we can better support the infant's fragile neurologic system to minimize these impairments can guide in helping the infant to grow and thrive within the artificial extrauterine environment of the NICU. Part of this support is the adoption of the conceptual framework and philosophy of developmental care and neuroprotection. Neuroprotection has been defined as strategies capable of preventing cell death (McGrath, Cone, & Samra, 2011). Advances in neuroimaging and research have provided broader insight into third trimester brain development, and what traditionally has been viewed as simply developmentally supportive care is now recognized to be neuroprotective care (Altimier & Phillips, 2016; Discenza, 2015; McGrath et al., 2011). Validating benefits of developmental care has been difficult because it is practiced in so many variations in different settings (Montirosso et al., 2016).

The pioneering work by Brazelton and Als found that assessing the individual infant's ability to cope with excessive stimulation provides the caregiver information to modify each infant's environment and treatment strategies with the goal to minimize excessive stimulation that is found to cause physiologic instability (Als, 1986; Brazelton, 1974; Brazelton, Parker, & Zuckerman, 1976). Infants born prematurely have demonstrated markedly improved outcomes when the stress of environmental overstimulation is reduced, and family bonds are supported. This can be accomplished by creating a supportive NICU environment utilizing innovative NICU design and by incorporating neuroprotective care into the care of high-risk neonates and their families. Neuroprotective interventions (NPI) in the NICU are strategies used to support the developing brain or to facilitate the brain after a neuron injury in a way that allows it to heal through developing new connections and pathways for functionality and by decreasing neuronal death (Altimier & Phillips, 2013, 2016; Pickler et al., 2010). NPIs that promote normal development and prevent disabilities include organizational, therapeutic, and environment-modifying measures, such as family-centered developmental care (Altimier & Phillips, 2013, 2016). Along with the caregiving environment, the physical environment, including space, activity, temperature, humidity, smell, noise, and light, has an impact on infant development (Altimier, 2015). Zeitgebers, timekeeping cues given by the environment such as a change in light or temperature, function to regulate the internal body clock (White, 2017).

The Neonatal Integrative Developmental Care Model describes seven core measures of neuroprotective family-centered developmental care to support preterm infant development: (1) healing environment (physical, sensory, and emotional), (2) positioning and handling, (3) partnering with families, (4) minimizing stress and pain, (5) safeguarding sleep, (6) protecting skin, and (7) optimizing nutrition. Neuroprotective care related to each core measure is outlined by Altimier and Phillips (2013, 2016). Each core measure has a related standard with defined infant characteristics, measurable goals, and corresponding NPIs. Although there are multiple models of developmental care, a common feature of each is the recognition that fragile preterm and sick infants and their families benefit from a specialized environment and care practices that have been adapted to their specific developmental needs.

PROVIDING A HEALING ENVIRONMENT

The optimal healing environment for any infant is physical contact with his/her mother. Every effort should be made to keep mothers and newborns together in skin-to-skin contact (SSC) whenever possible. This is the developmentally expected habitat for all newly born infants where they can be coregulated by their mothers to achieve ongoing physiologic stability. Unless the infant or mother is medically unstable, this environment provides the greatest level of support for optimal growth and development of preterm infants. In addition to the presence of an infant's mother (or other primary caregiver), a healing environment encompasses the physical environment (space, privacy, and safety), the sensory environment (touch, temperature, tastes, smells, noise, and light), and the social environment (families and staff). When mother (or primary caregiver) cannot be present or SSC is not an option (for either maternal or infant reasons), even more attention must be given to the design and maintenance of the physical, sensory, and social environments.

The physical environment involves not only space but also characteristics of space that affect position, movement, and motor development. Privacy and safety are separate, but equally important are factors in the physical environment. The sensory environment includes the exposures and experiencing of touch/movement, temperature/thermoregulation, taste/gustation, smell/olfaction, noise/vocalization, and light/vision as well as nutritional and chemical exposure. All sensory stimuli carry social and emotional connections and characteristics, and, in addition to creating cortical changes, have direct effects in the areas of social and emotional learning and memory, especially in the limbic system, where stress regulation, memory processing, and emotional development occur. The social environment includes family and staff and involves their availability for touch and emotional connections. Positive attitudes of compassion, caring, and love or negative attitudes of fear, anxiety, or anger are perceived by staff, family, and even the infants themselves, and affect the quality of interactions in the NICU environment.

There is considerable interaction between and within the physical, sensory, and social environments, and they are differentiated only for the purpose of discussion about opportunities for improvement in creating a holistic healing NICU environment for preterm and sick neonates and their families. Adverse physical, sensory, or social environmental factors can significantly interfere with growth, health, and appropriate neurodevelopment and neuroprocessing and can lead to lifelong alterations in function and well-being (Graven & Browne, 2008), while a carefully designed, healing environment can provide the support needed for optimal physical, mental, and emotional development (White, 2011).

The Physical Environment—Space, Privacy, and Safety

In 1976, the March of Dimes published *Toward Improving the Outcome of Pregnancy*, a landmark publication written by a multidisciplinary committee to provide a rationale, plan, and policy for regionalized perinatal care, as well as details of facility design and staff roles. In 1992, a multidisciplinary NICU Committee, under the auspices of the Physical and Developmental Environment of the High-Risk Infant Project, reached consensus on the first edition of recommended standards for NICU design. The purpose of this committee was to provide healthcare professionals, architects, interior designers, state healthcare facility regulators, and others involved in the planning of NICUs with a comprehensive set of minimum standards based on clinical experience and an evolving scientific database. The intent was to optimize design within the constraints of available resources and to facilitate excellent healthcare for the infant in a setting that supports the central role of the family and the needs of the staff. This group recognized that one way to promote the ideals of neurodevelopmental care and family-centered care (FCC) is through appropriate environmental modifications or construction of new NICU facilities. NICU design should meet the neurodevelopmental needs of the infants, provide adequate space and facilities for FCC, and meet the needs of the NICU staff. This committee has continued to update the NICU design standards with the latest recommendations published in 2013 that are available at https://nicu.science.nd.edu/stan%206.html (White, Smith, & Shepley, 2013).

When designing a NICU's physical environment, attention should be given to the NICU configuration, the location within the hospital, minimum space, clearance, and privacy requirements for the infant space. Family, staff, administrative, and general support space also needs to be delineated. Attention should focus on illumination guidelines (ambient, day lighting, and procedural) and acoustic guidelines (floor, wall, and ceiling surfaces). Electrical, gas, mechanical, isolation, ambient temperature, humidity, and ventilation recommendations likewise are outlined in the recommended standards. While the Facility Guideline Institute (FGI) provides guidelines for hospitals that serve as building requirements for NICU design, the guidelines lack sufficient detail to aid in many design decisions such as the rationale behind why a recommendation is being included. The Recommended Standards for Newborn ICU Design aim to address the gaps in guidance by providing interpretations of the standards, which include contextual information for why the design features are important (FGI, 2018a; White, 2013).

Research supports the concept that NICU design impacts outcomes. One systematic review collectively linked a range of aspects of the physical environment of the NICU to the well-being of patients, family comfort, and the caregiving process. Single-family rooms (SFRs) were deemed superior compared to open-bay units for patient care and parent satisfaction (Domanico, Davis, Coleman, & Davis, 2011). Others have demonstrated improved outcomes including increased privacy, increased parental involvement in patient care, improved noise control, improved sleep, decreased length of hospital stay, decreased rehospitalizations, reductions in costly hospital acquired infections, and lower direct costs of care (Julian et al., 2015; Ortenstrand et al., 2010; Sadatsafavi, Niknejad, Shepley, & Sadatsafavi, 2017; Shahheidari & Homer, 2012; Stevens et al., 2014).

When considering NICU design and unit configuration, it is important to remember that families and staff have different needs (M. Dunn, MacMillan-York, & Robson, 2016). Family needs include an emphasis on privacy and individualized care, whereas staff needs often emphasize efficiency and visibility. Parents prefer the intimacy of a SFR and the quieter atmosphere with decreased noise levels. Research shows that parental presence and holding in the NICU may promote healthy attachment and improve early neurobehavior in preterm infants and the SFR provides an environment that supports longer parental stays (Barton & White, 2016; Reynolds, Duncan, & Smith, 2013). High maternal involvement is associated with improved 18-month neurodevelopmental outcome, especially in infants cared for in a SFR NICU (Lester et al., 2016). In a study by Vohr et al. (2017), infants cared for in SFR NICUs had higher Bayley III cognitive and language scores, higher rates of human milk provision at 1 and 4 weeks, and higher human milk volume at 4 weeks (Vohr et al., 2017).

On the other hand, staff working in SFRs expressed concerns about higher workloads due to decreased visibility of infants as well as diminished opportunities for staff interaction and communication (Doede, Trinkoff, & Gurses, 2018).

Beacon Children's Hospital in South Bend, Indiana, unveiled their new innovative NICU in 2017, which consists of beautiful, spacious, and functional SFR NICU rooms. The SFRs have a number of elements that promote improved sensory development for the baby and family participation in care, which is the primary purpose for the SFR.

- Every patient room has a window. This is an important feature that helps maintain circadian rhythms for the baby, parents, and staff. Research shows that views of nature reduce stress and provide positive distraction for parents who may be distraught or depressed.
- Every SFR includes a family area with a toilet and shower that supports longer stays for family, encouraging their involvement in the care of their child.
- An interior garden courtyard is available that provides daylight and views of nature into the center of the unit.

Beacon Children's took the SFR concept a step further by introducing a new multipurpose patient care room called the NIC2 room. The innovative NIC2 room allows for couplet care (care for the postpartum mother and the NICU infant) to occur in the same room, eliminating separation. This facilitates early bonding of the mother with the child, which historically has been limited during the first few days of the baby's life. At the center of every room, at the baby's bedside, is a kangaroo chair—a specialized recliner that allows the mother to lean back and hold her baby(ies) safely, skin to skin. The NIC2 rooms have multiple purposes and functions beyond couplet care, such as accommodating multiples or group care, allowing for increased flexibility.

Like the SFR, the NIC2 room has a toilet room with a shower and sleeping space for two on a pull-out sofa bed. The toilet room has a sliding door, making it easy to access and reducing the inconvenience of the door swinging into the room. A breast pump is provided in every room, contained within the wardrobe on a dedicated shelf with a power outlet. Lockable drawers within the wardrobe are provided to secure personal valuables for the family. Also in the wardrobe is a refrigerator for the family to use. A separate refrigerator for breast milk is located on the counter at the footwall of the room in every SFR. The NIC2 room has two breast milk refrigerators in the event that two unrelated babies are in the same room.

All lighting in the room is dimmable for control over light levels at all times. No lights are located directly over the baby's bed, so that there is no chance of direct light shining into the baby's eyes. The procedure light is mounted to the headwall on an adjustable arm. Colored light-emitting diode (LED) lights at the footwall of the room, in a hue chosen by the family, will wash the wall with color to personalize the room. The color can be easily changed to vary the experience in the room and to suit the mood from day to day. Wall sconces in the family area of the room provide a soft level of light for reading or conversation. Two solid-surface shelves on the wall provide space for families to personalize the room for the baby.

Specific guidelines around SFRs are outlined in Standard 6 (White, Smith, Shepley, & Committee to Establish Recommended Standards for Newborns, 2013). The single-room NICU is a strategy that could address environmental concerns and minimize iatrogenic effects by reducing the risk of infection and stress on preterm infants while increasing opportunities for private parental interaction with their hospitalized infants. Whenever possible, a mother's arms should be the preferred locus of neonatal care (White, 2004). This concept has been enthusiastically endorsed by many and effectively applied in a number of healthcare settings. It is essential that the NICU be designed in such a way that families feel comfortable spending prolonged periods of time with their infant and encouraged to engage in intimate, nurturing encounters (M. Dunn et al., 2016).

The FGI: 2018 Guidelines for Design and Construction of Hospitals and Outpatient Facilities states that all patient rooms in the hospital setting must be single private rooms; yet, why then does the decision to build SFRs or bay/pod type rooms in the NICU remain controversial? Cost savings associated with SFR units should be justified in terms of clinical outcomes as well as construction and operation costs. Lester et al. (2014) have published compelling information regarding improved outcomes of NICU neonates, but only with appropriate developmental care in the SFR environment. Two types of cost must be taken into consideration when analyzing the implications for SFRs compared to open-bay/pod NICUs: onetime construction costs and ongoing operating costs. SFRs compared to a multiple-bed room design require an additional square footage per bed (minimum 165 square feet clear in the SFR vs. 120 square feet clear in the multiple-bed room), based on the Recommended Standards for Newborn ICU Design (White, 2013). These 45 net square feet per bed, or 67.5 gross square feet (GSF) using a 1.5 conversion factor, denotes the incremental difference between the two designs and does not imply that NICUs should be built to minimum standards for either multiple-bed or single-room design (Shepley, Smith, Sadler, & White, 2014). The amount of space allocated beyond the minimum should be equivalent for both designs based on a NICU's functional needs.

Direct costs of NICU care in SFRs have been found to be no greater than traditional open-bay/POD NICUs (Stevens et al., 2014). In a theoretical business plan for a SFR NICU, using data from two independent studies, Shepley et al. (2014) demonstrated that the cost of constructing a SFR NICU may be recuperated within the first 12 months of operation.

Ongoing operating cost in the predominantly SFR NICU entails a post-occupancy cost for increased heating and cooling. Larger NICUs required up to one additional Full-time equivalent (FTE) in support personnel but the nurse to patient ratio was not modified (Domanico et al., 2011; Sadatsafavi et al., 2017).

Specifications of materials used in the NICU also have an impact on the psychological, behavioral, physiologic, and environmental outcomes in the NICU. Selected finishes should focus on safety and the ambient environment to provide the psychological and physiologic outcomes for neonates, families, and caregivers. Mitigation of Hospital aquired infections (HAI) and unwanted sound is crucial to improving neonatal outcomes. Other outcomes, such as social support and the reduction of stress, anxiety, and fatigue, become attainable through the conscientious, evidence-based design in the NICU (Harris, 2016).

The number of NICUs designed to meet basic criteria for "green" design is increasing (Shepley, Song, & Marshall-Baker, 2016). LEED (Leadership in Energy and Environmental Design), a system authored by the U.S. Green Building Council along with the recommended standards for newborn ICU design, both provide information related to building a NICU with an environmentally sustainable design (U.S. Green Building Council, 2009). Several actions are important to accomplishing sustainable objectives (Gottlieb & Dickeman, 2007):

- Evaluating medical devices, building materials, and electronics
- Recycling and waste reduction
- Conserving energy

- Emphasizing sustainable foods
- Specifying green cleaning products
- Exploring the potential use of organic linens
- Addressing staff transportation and climate change
- Regulating pharmaceutical waste

Visual and physical access to nature and daylight are critical components of sustainability.

The U.S. Green Building Council also acknowledges the role of these environmental features and designates access to the natural environment as a source of points toward LEED certification.

While diurnal variation is important to the infants, the primary beneficiaries of the relationship with nature and daylight in the NICU are staff and families. For example, studies have revealed that family satisfaction is associated with the presence of gardens and nurses have preferences for access to natural conditions in lounge areas (Altimier, 2015).

The Sensory Environment

Defining the optimal sensory environment in the NICU is an elusive task. There is conflicting data on the dangers of both overstimulation and sensory deprivation in premature infants. Replicating the in utero environment is not possible in the NICU environment, nor is it the most appropriate thing to do. Continuation of the sensory environment found in utero can be disadvantageous to neurodevelopment of the preterm infant ex utero. For example, circadian rhythms are driven by endogenous processes and rely upon circadian time cues (zeitgebers) to remain appropriately oriented to the individual's environment and desired routine. The circadian rhythm of a fetus is guided by multiple maternal zeitgebers, none of which is readily available to the newly born infant. Instead, new zeitgebers must be established, most notably lighting cycles and breast milk (White, 2017). Accomplishing this is not as easy as turning a light on and off at the appropriate time of day, nor is the solution to simply leave the infant in a low-light environment continuously. Sensory deprivation of any sense (touch, movement, taste, smell, sound, or light) is clearly undesirable, as is overstimulation. It is also not as simple as getting the quantity of a particular stimulus right and giving it at the exact right time. Quality matters, and the target is continually moving, as the infant's medical condition, peripheral sensory apparatus, and brain maturity change almost daily (White, 2018).

Tactile/Touch and Temperature/Thermoregulation. One of the first principles of neonatal care is thermoregulation. At birth, the newborn infant moves from a warm fluid-filled intrauterine environment to a cooler dry environment. A major goal of neonatal care is to provide a thermoneutral environment in which an infant's basal metabolic requirements are minimized.

The physical environment (macroenvironment) should incorporate the following factors:

- Temperature: 72°F to 78°F (22°C–26°C)
- Relative humidity: 30% to 60%
- Six air changes per hour (with two from outside air)
- All air filtered with at least the efficiency specified in the FGI Guidelines (FGI, 2018b)

To enhance the development of the preterm infant, frequent attention is often on the thermoregulation (microenvironment) of the infant. The optimal environment for the infant is SSC with the mother, also known as kangaroo care (KC). SSC increases oxytocin levels in both mothers and fathers, a hormone known to induce relaxation, facial recognition, and bonding. SSC also increases prolactin levels in the mother, which is linked to increased breast milk production. Due to the close proximity to the mother's breasts, SSC is associated with higher rates of breastfeeding. Thermal synchrony is observed when mothers or fathers hold their babies in SSC, making it possible to warm a cool baby or cool an overly warm baby. Free unrestricted parental access is important to facilitate early and prolonged SSC and has been associated with higher KC rate as well as breast milk feeding rate (de Vonderweid & Leonessa, 2009).

When the parents are unavailable for SSC or SSC is not possible, thermoregulatory efforts should focus on the infant's individual bed space (microenvironment), whether it is a radiant warmer, incubator, or open crib. To maintain a constant central temperature within narrow limits (36.5°C–37.5°C), VLBW infants or premature infants need to be preferably cared for in a dual-function incubator or incubator (Altimier, 2012). The dual-function incubators include the incubator mode (closed-type incubator) and the radiant warmer mode (open-type incubator). This technology allows for care of a critically ill premature infant in a highly humidified environment (incubator mode), which can then be switched to the radiant warmer mode during a treatment, procedure, or for family space.

In addition to flexible modalities to ensure a thermoneutral environment, when considering incubators, attention should be given to those that have dramatically decreased decibel levels, further protecting the developing auditory system in the preterm infant. Covers specifically made for incubators are available to minimize light reaching the infant's eyes. Positioning an infant in a midline, flexed, and contained position with the assistance of therapeutic positioning aids and swaddling decreases the surface area of the infant exposed to environmental air, thus reducing radiant and convective heat losses. A flexed and contained position offers additional temperature stability for the infant by minimizing extraneous movement and energy expenditure (Altimier, 2012).

Chemosensory: Taste/Gustatory and Smell/Olfactory. Among all senses, from birth onward, olfaction plays a critical role in sensory communication. It allows the newborn to adapt its suckling and feeding behaviors, to be attracted to maternal odors, and to improve the mother–infant interactions. At term, only 25% of neurons in the olfactory bulb are mature and less than 10% of the olfactory tract is myelinated (Sarnat & Yu, 2015).

Providing supports for mothers and infants to be together early in the NICU stay is essential to support the gustatory and olfactory sensory development. Providing odor and taste of the mother's milk has been shown to facilitate the infant's mouthing, sucking, arousal, and calming from irritability, especially in preparation for oral feeding (Rattaz, Goubet, & Bullinger, 2005; Sullivan & Toubas, 1998). Providing a pacifier with mother's milk has been shown to increase nonnutritive sucking, intake, and growth and to shorten the length of hospitalization (Als et al., 2003; Bingham, Abassi, & Sivieri, 2003; Chaze & Luddington-Hoe, 1984). Providing multisensory experiences (when developmentally appropriate) such as combining odor and taste with proprioceptive and kinesthetic visual and auditory input can potentiate sensory organization during feeding. Holding the baby close to the caregiver's body serves to provide this organized multisensory environment (Browne, 2008).

The olfactory system is functional by 28 weeks' gestation (Liu et al., 2007). Olfaction (smell) is initiated by neural excitation in response to specific molecules in the immediate surroundings. Olfactory information (in the uterus for the fetus and at the breast for the neonate) is transmitted directly from the nose to the cerebral cortex. Maternal odor influences neonatal behavior (Milford & Zapalo, 2010). A mother's scent has been found to facilitate state regulation and optimal feeding experiences for both term and preterm infants. Since olfaction is functional in the second

trimester, sensory stimuli from the NICU environment rather than the mother may interfere with its development, as well as other sensory development and attachment (Schaal, Hummel, & Soussigan, 2004).

Neonates' sense of smell can be negatively stimulated by unpleasant odors. A variety of odorous products, such as cleaners, skin preparations, antibiotics, and alcohol (wipes and hand-gels), is often present in the typical NICU environment. The neonate can also be exposed to fragrances or aftershave worn by staff members. Infants may respond to noxious olfactory stimuli with altered respirations, transient apnea, and/or an increased heart rate (HR; Gardner & Goldson, 2002). The smell of NICU detergent, once detected by the neonate, elicits a response that decreases cerebral blood flow to the right hemisphere of the brain (Bartocci et al., 2000).

The emotional content of odors is highly plastic as it is modifiable by a few hours of mere exposure or by the pairings with reinforcers provided by caregivers (Liu et al., 2007). It has been shown that people can recall a scent with 65% accuracy after 1 year, because smells are processed by the same part of the brain that handles memories and emotions.

Enhancing the olfactory environment can be achieved through the utilization of olfactory NPIs. These positive NPIs may include maternal breast scent via a breast pad or a soft scent cloth. SSC helps support the discrimination of maternal breast scent. Mouth care provided with mother's milk helps the infant recognize the mother's smell and associates that smell with food and feeding when the infant is able to nipple feed.

Staff should not wear perfume, cologne, or aftershave in the NICU. Available unscented procedure preparation products should be used. Alcohol wipes should not be opened near an infant's head, and preferably outside of the incubator environment. Cleaning products utilized in the NICU should be unscented. Laundry services should also use unscented products. The odor of tobacco on caregiver bodies and clothing as well as the odors of dry-cleaning chemicals should be avoided. NICU staff and parents should be educated on this topic to prevent olfactory overstimulation.

Noise/Auditory. At birth, ears are capable of discerning more than 300,000 sounds. The brain processes sound a thousand times faster than images and registers sounds even during sleep. The constant bath of noise affects everything from concentration to health. The word *noise* comes from nausea, the Latin word for sickness. Excessive noise levels in the NICU can damage the developing cochlea and delicate auditory structures, especially the hair cells of the cochlea, resulting in hearing loss and arousal (Moon, 2011). Arousal is important with premature infants who are unable to inhibit responses. High noise levels in NICUs affect infants as well as staff and families. Loud transient noise has been shown to cause immediate physiologic effects such as increased HR, blood pressure, and respiratory rate (RR), apnea and bradycardia, hypoxia, and increased intracranial pressure (Wachman & Lahav, 2011). Noise also contributes to sleep disturbance, hearing impairment, and decreased oxygen saturation, which have a negative impact on nervous system development (Chen et al., 2009; Domanico, Davis, Coleman, & Davis, 2010; Graven, 2006; Krueger, Schue, & Parker, 2007).

Both the facility itself and operations occurring in the NICU impact the acoustical environment. Heating and ventilation systems are a challenge in a unit that attempts to provide private, separate areas that require a full ceiling-to-floor separation. From a budgetary perspective, it may substantially increase the cost of the unit renovation or construction. Those units that have met the fiscal and physical challenges of providing adequate ventilation have done so in an attempt to provide a more homelike atmosphere.

Much of the therapy provided in the NICU is noisy, making it difficult to facilitate developmentally beneficial auditory stimuli. These high noise levels are often a result of equipment, alarms, nonacoustical finishes, communication devices, and talking, as well as the underlying heating, ventilation, and air conditioning system. NICU sound levels vary based on the hour of day and are often related to activities such as shift change and medical rounds (Krueger et al., 2007). SFRs and larger clinical patient areas help reduce environmental noise because sound transmission declines geometrically as distances are increased (White, Smith, & Shepley, 2013).

The recommended guidelines for the acoustic environment state that infant rooms, staff work areas, and family areas shall be designed to produce minimal background noise and to contain and absorb as much transient noise as possible.

The combination of continuous background sound and operational sound in the infant area/room shall not exceed an hourly Local environmental quality (Leq) of 45 dB [decibels], an hourly L10 (noise level exceeded for 10% of the time of the duration of the measurement) of 50 dB, and transient sounds or Lmax (the RMS (root mean squared) maximum level of a noise source or environment) shall not exceed 65 dB, all A-weighted, slow response. In staff work areas, family area, and staff lounge areas, the combination of continuous background sound and operational sound shall not exceed an hourly Leq of 50 dB and an hourly L10 of 55 dB levels, both A-weighted, slow response. Transient sounds or Lmax shall not exceed 70 dB, A-weighted, slow response in these areas. (White et al., 2013)

Achieving these desired sound levels can help promote infant sleep and allow the baby to hear human voices at normal conversations (Philben, 2004). Although it is known that alarms and high-decibel sounds are not good, soothing sounds and talking to the preterm infant are critical to auditory processing and language development. Speech and language impairments of both simple and complex language functions are common among former preterm infants. Risk factors include lower gestational age and increasing severity of illness including severe brain injury. Even in the absence of brain injury, however, altered brain maturation and vulnerability imposed by premature entrance to the extrauterine environment is associated with structural and microstructural brain changes. These alterations are associated with language impairments with lasting effects in childhood and adolescence and increased needs for speech therapy and education supports (Vohr, 2014). Because nurses tend to be task oriented, this may need to be practiced to become "routine" during caregiving tasks (Bader, 2014).

One study by Pineda et al. (2012) showed that infants in SFRs with no parent present for significant periods of time were found to have decreased verbal scores after NICU discharge (Pineda et al., 2012). Caskey and colleagues showed that infants whose parents talked to them had increased vocalizations while in the NICU (Caskey, Stephens, Tucker, & Vohr, 2011).

Crowded rooms full of equipment can influence healthcare personnel's ability to provide environmentally appropriate care to premature infants. Noise levels of equipment have been a challenge to minimize due to industrial design standards and alarm management parameters; however, more companies are focusing greater attention on the noise levels generated by such equipment. Noise criterion ratings should be considered when selecting new equipment. Including this parameter into purchasing decisions is worthwhile.

Infant bed areas should be situated to produce minimal background noise and to contain and absorb as much transient noise as possible. Many sound control features should be considered when designing a NICU. Evidence-based sound-reducing strategies have been shown to decrease decibel levels by 4 to 6 dB when

planning environment management as part of a developmental, family-centered NICU (Byers, Waugh, & Lowman, 2006). Current air duct and ventilation systems should be evaluated for noise as well as dust. Acoustic ceiling tiles in direct patient care areas should have a noise reduction coefficient (NRC) rating of at least 0.90 for 80% of the entire surface area or an average NRC of 0.85 for the whole ceiling, including solid and acoustically absorptive surfaces (White et al., 2013). Porcelain sinks rather than stainless steel sinks can also minimize noise. Carpet decreases the noise level and promotes a homelike environment, yet rubber or vinyl flooring material directly at the bedside can ease the routine cleaning. Carpeting should be avoided in direct patient care areas, as well as around sinks and in clean and soiled utility rooms. One important issue is the noise created by the equipment used to clean the carpet. Utilization of a centralized vacuum system can limit noise levels and decrease dust levels. Other surfaces such as sound-absorbing wall surfaces and acoustical partitions may be used to additionally minimize noise (Altimier, 2015).

Thoughtful design of traffic patterns and workspaces can help remove a great deal of unwanted noise. Beds that are built in a pod design rather than down a long hall can reduce staff travel time as well as decrease noise levels for the beds at the near end of the hallway (White et al., 2013). Additionally, patient care supplies, linen, and trash placed strategically on walls that access the hallway through sliding cupboards/doors help reduce traffic into the patient room/care area.

Background sound levels in the NICU may interfere with an infant's ability to discriminate speech of parents and other caregivers. Neonates are also exposed to vibration and noise when transported and when on high-frequency ventilation. Noise and vibration combined may have a synergistic effect. Telephones audible from the infant area should have adjustable announcing signals. Noise can be limited through use of communication devices such as personal wireless phones that are set to vibrate. This technology minimizes the need for hardwired phones placed close to the infant and can reduce the need for beepers, overhead paging systems, and intercoms.

Dampening sounds from equipment, such as waste receptacles, sinks, paper-towel dispensers, and moveable equipment, is suggested for sound containment. Eliminating radios and all other unnecessary sounds, transferring infants from warmers to incubators with quiet motors as soon after admission as possible, and covering incubators with thick quilt/blankets with sound-absorbent material will also assist with sound abatement. Fire alarms in the infant area should be restricted to flashing lights without an audible signal. The audible alarm level in other occupied areas must be adjustable.

Music therapy has been used in some units to calm and soothe the environment. There is not enough evidence to say what source, type, intensity, or duration of music may be beneficial to preterm infants. With such an emphasis to achieve the quietest environment possible for the developing neonate, there is much uncertainty as to what, if anything, should be introduced to provide developmental benefit when the parents are not present.

Noise levels would be regularly monitored and reported to staff for self-assessment and to provide interventions and opportunities for improvement. Both intensity and duration of sound exposure should be considered when evaluating the noise level in a NICU. Some units are placing microphones in the ceiling above or on walls adjacent to infant care areas to determine the sound levels that are transmitted to the infant (decibel monitoring system). These microphones are wired to a monitoring device that feeds a signal to a visual alarm if the sound level exceeds a predetermined level. This visual system helps alert staff and parents to sounds that exceed a reasonable level and provides a gentle reminder to lower the sound level in order to provide a quietly healing environment for NICU infants, staff, and families.

Light/Vision. Protecting the development of the visual system is important because visual problems continue to be common among NICU graduates who were born prematurely. Visual stimulation is not required at any point before term gestation, since the visual system is the last sensory system to develop functionally at term. The eyelids and iris control the amount of light entering the eye. Infants at or before 32 weeks' gestation have thin eyelids and little or no pupillary constriction, thus allowing light to reach the retina much easier than more mature infants, children, and adults (Graven, 2011; LeVay, Wiesel, & Hubel, 1980). At 29 to 30 weeks' gestation, sleep partitions into rapid eye movement (REM) and non-REM (NREM; slow-wave) sleep. Transition to regular sleep occurs around 30 to 34 weeks' gestation (Graven, 2011). Protecting sleep cycles, and especially REM sleep periods, is critical for healthy visual development as any event or drug that disrupts REM sleep can impact visual development.

Endogenous brain activity stimulation (activity-independent) is created by spontaneous firing of neural cells in the retina, lateral geniculate nucleus (LGN), spinal cord, hippocampus, pons, cerebellum, cerebral cortex, and auditory systems, which occurs at a particular time in their development. The endogenous stimulation of the visual system prepares the retina, LGN, and visual cortex for exogenous or outside stimulation (Graven, 2006).

At 40 weeks' gestation, the human visual system has intact retinal development and pathways to the visual cortex. It is at this time that the visual system must have regular visual stimulation. Visual experiences for healthy visual development require ambient light (not direct light), focus, attention, novelty, movement, and, after 2 to 3 months, color (Graven, 2006). The visual system develops in utero in the total absence of light, and therefore the visual system is not developmentally ready for external visual stimuli until birth at term. Three main areas of care in the NICU that can adversely affect visual development are interference with endogenous brain cell activity, sleep deprivation, and intense light exposure.

Lighting in the NICU should be adjusted to support each infant's best sleep and awake organization and to deliver care without impinging on the development, comfort, and care of other infants (Lawhon & Als, 2010). Lighting in the NICU needs to be adjustable to the infant's developmental stage with a balance between dimmed ambient lighting, natural lighting, and brighter task lighting. A preterm infant should never be positioned facing directly into a light source. Only indirect ambient lighting should be utilized for preterm infants who cannot block out light through their thin eyelids, may not be able to turn away from light, and cannot communicate their needs (Rodríguez & Pattini, 2016; White et al., 2013). The focus of care for preterm infants of 22 to 28 weeks' gestation and/or VLBW infants should be on protecting the eyes from direct light and keeping ambient light exposure to low levels. Care of the 28 to 36 weeks' gestation preterm infants should focus on protecting sleep cycles, especially REM sleep. During this time, intense stimulation from NICU noises, vibrations, and other disturbing stimuli of other sensory systems can greatly interfere with the processes of visual system development (Lickliter, 2011).

Ambient lighting levels in the infant care spaces shall be adjustable through a range of at least 10 to no more than 600 Lux (the international symbol unit of illuminance), with a color rendering index (CRI) greater than 80 and a gamut area index (GAI) greater than 80 and less than 100. Both natural and electric light sources need to have controls that allow immediate, sufficient darkening of any bed space for transillumination when necessary. No direct view of the electric light source or sun shall be permitted in the

infant space. Use of multiple switches with individual dimmers to allow different levels of illumination is helpful. Procedural lighting should be available at each bedside to allow caregivers to evaluate a baby or to perform a procedure. This increased illumination should not increase light levels of adjacent babies. Illumination of support areas such as charting areas, medication preparation areas, and reception areas should be adequate to allow important or critical tasks to be performed. This light level should conform to Illuminating Engineering Society specifications (www.iesna.org). When possible, independent controls should be used to accommodate sleeping infants and working staff (Rea & Figueiro, 2016; White et al., 2013).

Each infant room, care area, or adjacent staff work area should have at least one source of daylight visible. Windows provide a psychological benefit to NICU staff as well as families. Day lighting is desirable for charting as well as the evaluation of infant skin tone. Exterior windows provide the recommended natural light and assist with diurnal cycling. However, serious problems with radiant heat loss or gain and glare can occur if infants are placed too close to external windows. External windows should be at least 2 feet away from the infant's bed and may be placed away from direct patient areas—for example, high up on the walls, as skylights, or in other locations that provide indirect light to the patient area. The latter might be a window in a hallway that secondarily allows light to pass into the NICU. All windows, including skylights, should have retractable covers for times when light is not desired. These windows should be insulated and have shading devices in a neutral color to minimize color distortion from transmitted light. Significant flexibility in lighting levels is required to accommodate the disparate needs of infants at various stages of development and at various times of the day, as well as the needs of caregivers.

Safeguarding Sleep

Sleep is a crucial human physiological need, which is beneficial to the maturation of the central nervous system memory consolidation, secretion of growth hormone (Als et al., 1994; Bonan, Pimentel Filho, Tristão, Jesus, & Campos Junior, 2015), energy storage, and illness recovery (Mahmoodi, Arbabisarjou, Rezaeipoor, & Pishkar Mofrad, 2015). The disruption of sleep experienced by preterm infants in the NICU may influence brain development and result in negative neurobehavioral outcomes, especially in learning and memory (Bonan et al., 2015; Valeri, Holsti, & Linhares, 2015). The chaotic environment of the NICU can interfere with infants' ability to modulate their sleep–wake states (Als, 1986). Preterm infants need caregivers' assistance in regulating their sleep–wake states by reducing environmental stress and adjusting nursing care activities (Als, 1986). Therefore, it is important to develop supportive interventions to facilitate infants' sleep in order to mitigate the negative influences of sleep disruption in the NICU.

Sleep organization begins during fetal life, at which time it is influenced by multiple maternal zeitgebers (White, 2018). Preterm infants are deprived of these maternal factors, so they develop a sleep structure based on the environment of the NICU. Preterm infants typically sleep less and have seriously disrupted and fragmented patterns of sleep (Levy et al., 2017).

In neonates, the sleep cycle is frequently categorized into three stages: active, quiet, and indeterminate sleep. Quiet sleep plays a role in energy restoration and cerebral maturation, in particular in the development of thalamocortical and cortical pathways and synaptogenesis. It allows stabilization of neuronal connections, increases protein synthesis, and releases growth hormones. Active sleep is characterized by a high level of endogenous neuronal activity. It contributes to the maturation of the central nervous system and the consolidation of memory and axonal connections, especially between the retina and the brain, and is accompanied by REM (Graven, 2006; Tarullo, Balsam, & Fifer, 2011).

Zores et al. (2018) found that small light-level increases led to sleep disruption in very preterm infants. Combined with our previous results, which documented the physiologic responses of very preterm infants to changes in light levels, these findings clearly demonstrate that very preterm infants are visually sensitive to small changes in light levels. Notably, these behavioral and physiologic responses occurred when there were small light-level changes that were within the light-level range recommended by the American Academy of Pediatrics. The main determinant of awakening was the initial light level. The physiologic and behavioral responses were greater, and awakening events were more common under medium light protection rather than high light protection conditions. Thus, very preterm infants reacted more strongly to a small change in light level when the baseline light level was greater. Further studies are needed to more precisely determine the mechanism by which the properties of the visual stimulus influence the reactivity of infants (Zores et al., 2018). Additionally, the Cochrane review on cycled lighting included randomized controlled trials that further demonstrated improved outcomes for infants in a cycled lighting environment (Morag & Ohlsson, 2016).

At approximately 28 weeks' gestation, individual sleep patterns begin to emerge characterized by REM and NREM sleep periods. These periods become constant by 36 to 38 weeks' gestational age. REM sleep dominates in the initial sleep cycles; REM and NREM are nearly equal as the infant approaches term, and by 8 months of age NREM sleep occupies nearly 80% of sleep time (Hobson, 1995). REM and NREM sleep cycling are essential for early neurosensory development, learning and memory, and preservation of brain plasticity for the life of the individual (Graven, 2006). For the visual system, the need for visual experiences does not occur until near term or 40 weeks' gestational age. The environment of the fetus in utero and the preterm infant in the NICU require appropriate levels of specific types of neurosensory stimuli for healthy early brain development (Graven, 2006; Graven & Browne, 2008).

Preservation of "brain plasticity," the ability of the brain to constantly change its structure and function in response to environmental changes, is an essential process throughout childhood and adult life. Sleep deprivation (both REM and NREM) results in a loss of brain plasticity, which is manifested by smaller brains, altered subsequent learning, and long-term effect on behavior and brain function. Facilitation and protection of sleep and sleep cycles are essential to long-term learning and continuing brain development through the preservation of brain plasticity (Graven & Browne, 2008).

Because REM sleep is essential for neurosensory as well as visual development, neuroprotective strategies for the NICU infant include the following:

- Protect the eyes from direct light exposure and maintain low levels of ambient light when not needed for care and procedures
- Provide some daily exposure to light, preferably including shorter wavelengths, for entrainment of the circadian rhythm (after 28 weeks' gestation; Rivkees, Mayes, Jacobs, & Gross, 2004)
- Protect sleep cycles, and especially REM sleep; avoid sleep interruptions, bright lights, loud noises, and unnecessary physical disturbing activities
- Avoid high doses of sedative and depressing drugs, which can depress the endogenous firing of cells, thus interfering with visual development, REM, and NREM sleep cycles
- Provide developmental care appropriate for the age and maturation of the infant (Graven, 2011).

Continuous bright lights in the NICU can disrupt sleep–wake states. Patients of any age who are trying to sleep find direct light unpleasant. Premature infants are photophobic; however, they will open their eyes with dim lights. If the light levels never change, infants never experience the diurnal rhythm necessary for development. Reducing light levels may facilitate rest and subsequent energy conservation and promote organization and growth.

Special attention should be given to lighting as it relates to caregivers who work night shifts. Visual and circadian needs of staff are quite different from those of patients. Five characteristics of light important for both human visual and circadian systems are quantity, spectrum, timing, duration, and distribution. The visual system responds well to a light stimulus at any time of the day or night and does not depend on the timing of light. Timing of the light exposure, however, is critical for circadian development. The visual system responds to a light stimulus in milliseconds; yet, the duration of light exposure necessary to stimulate the circadian system can take minutes (Figueiro & White, 2013).

Most babies should remain in a dimly lit environment at night, yet some staff may have difficulty staying alert, which could cause safety concerns. Shift-work disorder, a circadian sleep dis-order characterized by sleepiness and/or insomnia, is associated with decreased productivity, impaired safety, diminished quality of life, and adverse effects on health, such as increased risk for metabolic syndrome, diabetes, cardiovascular disease, ischemic stroke, depression, obesity, gastrointestinal dysfunction, reproductive problems, and cancer (Antunes, Levandovski, Dantas, Caumo, & Hidalgo, 2010; Figueiro & White, 2013). Both the health of caregivers and the safety of infants need to be considered with all unit designs.

Light levels should be regularly monitored and reported to staff for self-assessment and to provide interventions and opportunities for improvement. Both intensity and duration of light exposure should be considered when evaluating the light levels in a NICU. Some units are placing visual sensors in the ceiling above or on walls adjacent to infant care areas to determine the light levels that are transmitted to the infant. This can help alert staff and parents to light levels that exceed a reasonable level and provides a gentle reminder to lower the light level in order to provide a dimmed healing environment for NICU infants, staff, and families.

Positioning and Handling

Even as we focus on the macroenvironment in most of this chapter, we cannot forget about the microenvironment. Positioning (or nesting) the neonate in midline, flexion, and containment is one of the most important NPIs that minimizes the effect of environmental stimuli from the NICU, thereby promoting comfort and sleep. Nesting facilitates transformation of the sleep pattern from erratic disturbed spells to deep peaceful periods of sleep, which has shown to conserve energy and minimize weight loss. A study by Mony, Selvam, Diwakar, and Raghavan (2018) observed the effect of nesting on sleep pattern among preterm infants admitted in NICUs.

Results demonstrated a significantly higher (113 minutes) total duration of sleep time among infants with nesting as compared to routine care (86 minutes), which is highly significant ($t = 4.930$, $p < .001$; Mony et al., 2018).

Minimizing Stress and Pain

Preterm infants typically cared for in NICUs undergo repeated invasive procedures, which can result in pain and stress, and, in turn, disturb infants' sleep cycles and sleep quality, all of which influence their growth and overall health (Bonan et al., 2015; Lan et al., 2018; Liaw et al., 2013; Ranger & Grunau, 2014; Valeri et al., 2015).

Greater numbers of painful procedures in preterm infants (gestational age ≤29 weeks) are associated with delayed postnatal growth, poor early neurodevelopment, high cortical activation, long-term abnormalities in white matter microstructure, brain development, and lower IQ in toddlers born very preterm (gestational age ≤32 weeks; Valeri et al., 2015). Furthermore, greater numbers of painful neonatal experiences cumulatively have been associated with a poor quality of cognitive and motor developments at 1 year of age and changes in cortical rhythmicity and cortical thickness in children at 7 years of age (Valeri et al., 2015). The utilization of supportive care bundles (modulation of the infants' states, nonnutritive sucking, facilitated tucking, and oral sucrose) during intrusive procedures not only significantly increases sleep efficiency and total sleep time, but also significantly decreases duration of sleep latency and frequency of wake bouts (Lan et al., 2018).

The Social Environment—Staff and Family Partnerships

The admission of an infant to the NICU is frequently a crisis for the family. The delivery is usually unexpected, and the family unit is often separated. Their infant is attached to wires, cables, and equipment in a harsh NICU environment that is far different from the newly decorated home nursery they had planned. The environment can become comforting and inviting with attentive and compassionate caregivers who provide a welcoming environment to initiate effective partnerships with parents.

The concept of partnering with families in the NICU offers a philosophy of care acknowledging that, over time, the family has the greatest influence over an infant's health and well-being. Creating an effective partnership between professionals and families has shown benefits such as decreased length of stay (LOS), increased satisfaction for both staff and parents, and enhanced neurodevelopmental out comes for infants (Segers, Ockhuijsen, Baarendse, van Eerden, & van den Hoogen, 2019). A recent study by Welch et al. (2017) strengthened the conclusion that family-nurturing interventions (FNI) promote cerebral cortical development of preterm infants.

Establishing family–professional partnerships in the NICU environment can be challenging; yet, because families are the constant in the infant's life, helping families achieve a positive outcome from their NICU experience should be a priority while providing care. The family is integral to developmental care, and NICU design should include accommodations and considerations for the comfort and support of families. Parents must be viewed as partners in the care of their infant, rather than visitors to the NICU, and spaces should be created in the NICU environment that are welcoming and encourage their presence in the NICU and participation in their baby's care. Consideration should be given to attractive and clear signage in the primary languages spoken by the populations served by the hospital. Adequate and convenient storage of personal belongings should be made available to parents who will spend considerable time in the NICU. Comfortable chairs should be present at every bedside to facilitate prolonged SSC between parents and infants as early SSC is associated with a reduced risk of bronchopulmonary dysplasia (BPD) development, cholestasis, and nosocomial infections (Casper, Sarapuk, & Pavlyshyn, 2018). Providing parents with computer and Internet access and educational materials as well as space for parents to socialize supports the emotional and psychosocial needs of NICU parents. It is ideal to have spaces with equipment for parents to make meals, wash clothes, shower, and sleep in close proximity to their NICU baby. Private spaces for therapeutic interactions with

NICU mental health providers will facilitate psychosocial supportt for NICU parents who are at significantly increased risk for postpartum depression, anxiety disorders, and posttraumatic stress disorder.

The well-being of NICU staff is equally important. NICU staff often suffer from caregiving fatigue and secondary posttraumatic stress. Prioritizing equipment and workspace in the NICU design that optimizes staff workflows will support NICU staff in providing the best care with the greatest efficiency. NICU design that includes spaces for rest and relaxation in a pleasant environment during work breaks will give NICU staff tangible evidence of the value placed on their well-being.

Promoting a healing social environment requires a NICU design that prioritizes the need to support all members of the multidisciplinary team involved in caring for preterm and sick infants in the NICU, including medical, nursing, therapy staff, and parents. Equilateral respect and support among all members involved in this partnership will promote optimal patient care, enhance family satisfaction, and engage the healthcare team.

THE FUTURISTIC NICU

Premature and ill full-term infants require complex, real-time, clinical decision support correlating medical data from multiple sources as there are many potential complications of prematurity.

Neonatal intensive care is a complex environment that must support collaborative decision making among various care providers. Clinical decision support utilizing "Big Data" in the NICU can benefit from online health analytics platforms that leverage high-speed physiologic data together with other electronic health record data (McGregor, 2013).

Infants in the NICU are frequently attached to many different medical devices, such as cardiorespiratory monitors, mechanical ventilators, temperature probes via incubators, smart infusion pumps, and neurologic monitors, all of which display constantly changing sensed data, usually at second-by-second intervals, generating over a billion data points per patient per day. Caregivers, typically NICU nurses, must translate this data into actionable information.

Recent and upcoming technologies are changing how we deliver neonatal intensive care and how we support babies and their parents through their NICU journey. Technology has long been the backbone of modern neonatal intensive care, yet with the overwhelming amount of data generated by technology and electronic medical records, there is a need to view the infant and infant parameters more holistically in order to support clinical decision making. Clinical rule-based engines and deep learning combined with comprehensive integrated platforms can address current issues of NICUs, such as tedious workflows and the integration of big data generated by multiple devices at once.

SUMMARY

The NICU is where an extraordinary period of growth and development will take place for premature infants. Because the preterm infants are no longer protected in the uterus, their physiologic and neuroprotective needs have dramatically changed. In order to meet the unique developmental needs of preterm and sick neonates, efforts must be made to modify the usual hospital environment to create a specialized healing environment that supports their ongoing neurosensory and neurobehavioral development. Whenever possible, the optimal healing environment for infants in the NICU is in SSC with their mothers (or other primary caregivers), but also encompasses the physical environment (space, privacy, and safety), the sensory environment (touch, temperature, tastes, smells, noise, and light), as well as the social environment (families and staff). While aiming for a gentler approach, we should always assess and reevaluate our treatments and routines, because sometimes "less" is best, while at other times, "less" might not be enough.

CASE STUDY

■ Identification of the Problem

- 24-week gestational age newly born premature infant girl weighing 650 g

■ Assessment: History and Physical Examination

Upon delivery, the infant was limp, cyanotic/pale, and apneic. The infant was successfully resuscitated following Neonatal Resuscitation Program© (NRP) guidelines; required 2 minutes positive pressure ventilation by T-piece resuscitator to initiate effective ventilation when spontaneous respirations were noted; infant received 10 minutes of continuous positive airway pressure (CPAP) via the T-piece resuscitator, prior to being transferred to the NICU.

■ Physical Examination on Admission to the NICU

- TEMPERATURE: 35.7°C, axillary HR 180 beats/min; RR: 56, shallow; saturations 88% to 92% in room air
- HEENT: WNL
- RESPIRATORY: lung fields bilaterally clear and equal to bases; grunting
- CARDIOVASCULAR: rate regular with no murmur noted; good peripheral perfusion, capillary blood refill less than 3 seconds, and strong peripheral pulses noted
- ABDOMEN: abdomen soft, flat, and nontender with no masses palpable; three-vessel cord; the anus appeared patent
- GENITOURINARY: normal female infant genitalia
- NEUROLOGIC: appropriate responses, eyes open and infant blinks; extremities well formed; decreased muscle tone
- SKIN: pale pink, thin, transparent, yet intact skin
- EXTREMITIES: well formed; 10 digits per extremity; low tone
- Umbilical arterial and venous catheters were placed for fluid management and laboratory specimen draws

■ Differential Diagnoses. The differential diagnosis includes the following:

1. Prematurity
2. Perinatal hypoxic-ischemic injury
3. Shock
4. Congestive heart failure
5. Sepsis screen

■ Diagnostic Tests. Head ultrasound at 24 hours of age

■ Working Diagnosis. Extreme prematurity

■ Development of Management Plan

- Place infant in 80% humidified incubator
- Position infant in midline, flexed, and contained position utilizing positioning aids (e.g., Snuggle Up, bendy)
- Continuously monitor vital signs (VS), every 2 to 4 hours

- Maintain fluid support; TPN (total parenteral nutrition) within 24 hours of life
- Provide respiratory support with CPAP as needed
- Administer antibiotics until cultures negative for 72 hours

■ Implementation and Evaluation of Effectiveness

Implementation of Management Plan (Immediately After Initial Assessment in the NICU)

- Mother was transferred with infant to a Couplet Care Room for her care as well as the care of her infant with father assisting
- Infant was placed on CPAP of 5 within the first half hour of life

■ Effectiveness of Management Plan

- Temperature was 36.7 at 1 hour of life
- Respiratory status was stable by 2 hours of life
- Blood pressure was normal within 2 hours of life

■ Outcome

Extremely premature white female infant with stable VS. Anticipate lengthy NICU stay. Neuroprotective family-centered developmental care will be individualized to meet the infant's and family's needs at each developmental stage. Exogenous stimuli will be limited, with positive neuroprotective strategies introduced as tolerated and warranted.

EVIDENCE-BASED PRACTICE BOX

The design and operation of NICUs have evolved from the 1960s to the 2000s to support and accommodate the changes in technology involved in meeting the physical and caregiving needs of preterm infants and their families. The equipment has changed, the space has enlarged, and caregiving practices have changed. Units historically were designed as large, open areas with visibility for the caregivers. Infants were in rows, close to each other, with open space between bays. Technology has advanced with the ability to keep smaller and smaller infants alive. Small infants, less than 1,500 g, occupy most patient days, with many stays being 3 months and longer. Although the survival rate has improved, the number of infants with evidence of neurologic and learning problems continues to increase.

The focus on the environment of preterm infants and young neonates began in the 1970s but made little progress in changing the environment of the fetus or infant until the 1990s. Even in 2019, it is estimated that less than half of the more than 1,500 NICUs in the United States and even fewer in Europe and Asia are able to maintain an environment and care practices that are supportive of early neurosensory and neuromotor brain development. These units support the physiology of care, but many fail to support the needs for healthy brain development.

Although preterm birth accelerates the maturation of the lungs, kidneys, and gastrointestinal tract, it does not accelerate neuroprocesses, and under most conditions of care, it can seriously alter these processes. Processes under genetic control are thought to be important but not altered by the environment. With the studies of epigenetics, it is now clear that environmental factors can alter the expression of genes related to brain development without altering the DNA structure or code for the gene.

Alterations in the sensory environment including excess noise, bright lights, sleep deprivation, and poorly timed caregiving all affect neurosensory development in the preterm infant. The physical environment, the nutritional environment, and the social/emotional environment also influence the processes involved in the early development of the neurosensory systems. Neuroprotective family-centered developmental care provided in an environment that supports early brain development is essential for optimal outcomes and the best possible long-term development. It is essential that NICUs make changes necessary to have a healing environment along with care practices that support and protect the processes of early brain development (Altimier & White, 2014; White, 2013).

References

Altimier, L., & White, R. (2014). The neonatal intensive care unit (NICU) environment. In C. Kenner & J. Lott (Eds.), *Comprehensive neonatal nursing care* (5th ed., pp. 722–738). New York, NY: Springer Publishing Company.

White, R. D. (2013). Recommended NICU design standards and the physical environment of the NICU. *Journal of Perinatology, 33*(Suppl. 1), S1. doi:10.1038/jp.2013.9

ONLINE RESOURCES

Recommended Standards for Newborn ICU Design. Retrieved from https://nicu.science.nd.edu/stan%206.html

REFERENCES

Als, H. (1986). A synactive model of neonatal behavioral organization: Framework for the assessment and support of the neurobehavioral development of the premature infant and his parents in the environment of the neonatal intensive care unit. *Physical & Occupational Therapy in Pediatrics, 6*, 3–53. doi:10.1080/J006v06n03_02

Als, H., Gilkerson, L., Duffy, F. H., McAnulty, G. B., Buehler, D. M., Vandenberg, K., . . . Jones, K. J. (2003). A three-center, randomized, controlled trial of individualized developmental care for very low birth weight preterm infants: Medical, neurodevelopmental, parenting, and caregiving effects. *Journal of Developmental and Behavioral Pediatrics, 24*(6), 399–408. doi:10.1097/00004703-200312000-00001

Als, H., Lawhon, G., Duffy, F. H., McAnulty, G. B., Gibes-Grossman, R., & Blickman, J. G. (1994). Individualized developmental care for the very-low-birth-weight preterm infant: Medical and neurofunctional effects. *Journal of the American Medical Association, 272*, 853–858. doi:10.1001/jama.1994.03520110033025

Altimier, L. (2012). Thermoregulation: What's new? What's not? *Newborn and Infant Nursing Reviews, 12*(1), 51–63. doi:10.1053/j.nainr.2012.01.003

Altimier, L. (2015). Neuroprotective Core Measure 1: The healing NICU environment. *Newborn and Infant Nursing Reviews, 15*(3), 91–96. doi:10.1053/j.nainr.2015.06.014

Altimier, L., & Phillips, R. M. (2013). The neonatal integrative developmental care model: Seven neuroprotective core measures for family-centered developmental care. *Newborn and Infant Nursing Reviews, 13*(1), 9–22. doi:10.1053/j.nainr.2012.12.002

Altimier, L., & Phillips, R. M. (2016). The neonatal integrative developmental care model: Advanced clinical applications of the seven core measures for neuroprotective family-centered developmental care. *Newborn and Infant Nursing Reviews, 16*(4), 230–244. doi:10.1053/j.nainr.2016.09.030

Antunes, L. C., Levandovski, R., Dantas, G., Caumo, W., & Hidalgo, M. P. (2010). Obesity and shift work: Chronobiological aspects. *Nutrition Research Reviews, 23*, 155–168. doi:10.1017/S0954422410000016

Azevedo, F., Carvalho, L., Grinberg, L., Farfel, J., Ferretti, R., Leite, R., . . . Herculano-Houzel, S. (2009). Equal numbers of neuronal and nonneuronal cells make the human brain an isometrically scaled-up primate brain. *The Journal of Comparative Neurology, 513*, 532–541. doi:10.1002/cne.21974

Bader, L. (2014). Brain-oriented care in the NICU: A case study. *Neonatal Network, 33*(5), 263–267. doi:10.1891/0730-0832.33.5.263

Bartocci, M., Serra, G., Papiendieck, G., Mustica, T., Serra, G., & Lagercrantz, H. (2000). Cerebral cortex response in newborn infants after exposure to the smell of detergent used in NICU: A near infrared spectroscopy study. *Pediatric Research, 47*, 388A. doi:10.1203/00006450-200007000-00006

Barton, S., & White, R. (2016). Advancing NICU care with a new multi-purpose room concept. *Newborn and Infant Nursing Reviews, 16*(4), 222–224. doi:10.1053/j.nainr.2016.09.010

Bingham, P. M., Abassi, S., & Sivieri, E. (2003). A pilot study of milk odor effect on nonnutritive sucking by premature newborns. *Archives Pediatric Adolescent Medicine, 157*, 72–75. doi:10.1001/archpedi.157.1.72

Bonan, K., Pimentel Filho, J., Tristão, R., Jesus, J., & Campos Junior, D. (2015). Sleep deprivation, pain and prematurity: A review study. *Arquivos De Neuro-Psiquiatria, 73*(2), 147–154. doi:10.1590/0004-282X20140214

Bouyssi-Kobar, M., Brossard-Racine, M., Jacobs, M., Murnick, J., Chang, T., & Limperopoulos, C. (2018). Regional microstructural organization of the cerebral cortex is affected by preterm birth. *NeuroImage: Clinical, 18*, 871–880. doi:10.1016/j.nicl.2018.03.020

Brazelton, T. B. (1974). Does the neonate shape his environment? *Birth Defects Original Article Series, 10*, 131–140.

Brazelton, T. B., Parker, W. B., & Zuckerman, B. (1976). Importance of behavioral assessment of the neonate. *Current Problems in Pediatrics, 7*, 1–32. doi:10.1016/S0045-9380(76)80013-8

Browne, J. V. (2008). Chemosensory development in the fetus and newborn. *Newborn and Infant Nursing Reviews, 8*(4), 180–186. doi:10.1053/j.nainr.2008.10.009

Byers, J. F., Waugh, W. R., & Lowman, L. B. (2006). Sound level exposure of high-risk infants in different environmental conditions. *Neonatal Network, 25*(1), 25–32. doi:10.1891/0730-0832.25.1.25

Caskey, M., Stephens, B., Tucker, R., & Vohr, B. (2011). Importance of parent talk on the development of preterm infant vocalizations. *Pediatrics, 128*(5), 910–916. doi:10.1542/peds.2011-0609

Casper, C., Sarapuk, I., & Pavlyshyn, H. (2018). Regular and prolonged skin-to-skin contact improves short-term outcomes for very preterm infants: A dose-dependent intervention. *Archives De Pédiatrie: Organe Officiel De La Sociéte Française De Pédiatrie, 25*(8), 469–475. doi:10.1016/j.arcped.2018.09.008

Chaze, B., & Luddington-Hoe, S. (1984). Sensory stimulation in the NICU. *American Journal of Nursing, 84*, 68–71. Retrieved from https://www.jstor.org/stable/3463253

Chen, H.-L., Chen, C.-H., Wu, C.-C., Huang, H.-J., Wang, T.-M., & Hsu, C.-C. (2009). The influence of neonatal intensive care unit design on sound level. *Pediatrics and Neonatology, 50*(6), 270–274. doi:10.1016/S1875-9572(09)60076-0

Chorna, O., Solomon, J. E., Slaughter, J. C., Stark, A. R., & Maitre, N. L. (2014). Abnormal sensory reactivity in preterm infants during the first year correlates with adverse neurodevelopmental outcomes at 2 years of age. *Archives of Disease in Childhood–Fetal and Neonatal Edition, 99*(6), F475–F479. doi:10.1136/archdischild-2014-306486

de Vonderweid, U., & Leonessa, M. (2009). Family centered neonatal care. *Early Human Development, 85*(10, Suppl.), S37–S38. doi:10.1016/j.earlhumdev.2009.08.009

Discenza, D. (2015). Neuro-NICUs: Nurturing the tiniest of brains. *Neonatal Network, 34*(5), 291–293. doi:10.1891/0730-0832.34.5.291

Doede, M., Trinkoff, A., & Gurses, A. (2018). Neonatal intensive care unit layout and nurses' work. *Health Environments Research & Design Journal, 11*(1), 101–118. doi:10.1177/1937586717713734

Domanico, R., Davis, D. K., Coleman, F., & Davis, B. O., Jr. (2010). Documenting the NICU design dilemma: Parent and staff perceptions of open ward versus single family room units. *Journal of Perinatology, 30*(5), 343–351. doi:10.1038/jp.2009.195

Domanico, R., Davis, D. K., Coleman, F., & Davis, B. O., Jr. (2011). Documenting the NICU design dilemma: Comparative patient progress in open-ward and single family room units. *Journal of Perinatology, 31*(4), 281–288. doi:10.1038/jp.2010.120

Dunn, A. (2003). Brain challenge for premature babies. Retrieved from http://www.theage.com.au/articles/2003/11/28/1069825996785.html

Dunn, M., MacMillan-York, E., & Robson, K. (2016). Single family rooms for the NICU: Pros, cons and the way forward. *Newborn and Infant Nursing Reviews, 16*(4), 218–221. doi:10.1053/j.nainr.2016.09.011

Facility Guideline Institute. (2018a). *Guidelines for design and construction of hospitals*. Washington, DC: American Society for Healthcare Engineering of the American Hospital Association.

Facility Guideline Institute. (2018b). *Guidelines for design and construction of hospitals and outpatient facilities*. Washington, DC: American Society for Healthcare Engineering of the American Hospital Association.

Figueiro, M., & White, R. (2013). Health consequences of shift work and implications for structural design. *Journal of Perinatology, 33*(Suppl.), S17–S23. doi:10.1038/jp.2013.7

Gardner, S. L., & Goldson, E. (2002). The neonate and the environment: Impact on development. In G. B. Merenstein & S. L. Gardner (Eds.), *Handbook of neonatal intensive care* (5th ed., pp. 219–282). St. Louis, MO: Mosby.

Gorzilio, D. M., Garrido, E., Gaspardo, C. M., Martinez, F. E., & Linhares, M. B. (2015). Neurobehavioral development prior to term—Age of preterm infants and acute stressful events during neonatal hospitalization. *Early Human Development, 91*, 769–775. doi:10.1016/j

Gottlieb, M., & Dickeman, N. (Eds.). (2007). *First do no harm: Environmental responsibility in the NICU*. Burlinton: Vermont Oxford Network.

Graven, S. N. (2006). Sleep and brain development. *Clinics in Perinatology, 33*(3), 693–706. doi:10.1016/j.clp.2006.06.009

Graven, S. N. (2011). Early visual development: Implications for the neonatal intensive care unit and care. *Clinics in Perinatology, 38*, 671–683. doi:10.1016/j.clp.2011.08.006

Graven, S. N., & Browne, J. V. (2008). Sleep and brain development: The critical role of sleep in fetal and early neonatal brain development. *Newborn & Infant Nursing Reviews, 8*(4), 173–179. doi:10.1053/j.nainr.2008.10.008

Harris, D. (2016). Surface finish materials: Considerations for the Neonatal Intensive Care Unit (NICU). *Newborn and Infant Nursing Reviews, 16*(4), 203–207. doi:10.1053/j.nainr.2016.09.006

Hebb, D. (1949). *Foundations of psychological thought: A history of psychology*. Oxford, England: Wiley.

Hobson, J. (1995). *The development of sleep*. New York, NY: Scientific American Library.

Hutchon, B. (2018). Minor neurological dysfunction and other comorbidities in children born extremely preterm. *Developmental Medicine and Child Neurology, 60*(8), 737–738. doi:10.1111/dmcn.13905

Julian, S., Burnham, C., Sellenriek, P., Shannon, W. D., Hamvas, A., Tarr, P. I., & Warner, B. B. (2015). Impact of neonatal intensive care bed configuration on rates of late-onset bacterial sepsis and methicillin-resistant *Staphylococcus aureus* colonization. *Infection Control & Hospital Epidemiology, 36*(10), 1173–1182. doi:10.1017/ice.2015.144

Keunen, K., Counsell, S., & Benders, M. (2017). The emergence of functional architecture during early brain development. *Neuroimage, 160*, 2–14. doi:10.1016/j.neuroimage.2017.01.047

Krueger, C., Schue, S., & Parker, L. (2007). Neonatal intensive care unit sound levels before & after structural reconstruction. *The American Journal of Maternal Child Nursing, 32*(6), 358–362. doi:10.1097/01.NMC.0000298131.55032.76

Lan, H., Yang, L., Hsieh, K., Yin, T., Chang, Y., & Liaw, J. (2018). Effects of a supportive care bundle on sleep variables of preterm infants during hospitalization. *Research in Nursing & Health, 41*(3), 281–291. doi:10.1002/nur.21865

Lawhon, G., & Als, H. (2010). *Theoretical perspective for developmentally supportive care* (2nd ed.). Glenview, IL: National Association of Neonatal Nurses.

Lester, B., Hawes, K., Abar, B., Sullivan, M., Miller, R., Bigsby, R., . . . Padbury, J. F. (2014). Single-family room care and neurobehavioral and medical outcomes in preterm infants. *Pediatrics, 134*(4), 754–760. doi:10.1542/peds.2013-4252

Lester, B., Salisbury, A., Hawes, K., Dansereau, L., Bigsby, R., Laptook, A., & . . . Padbury, J. (2016). 18-Month follow-up of infants cared for in a single-family room neonatal intensive care unit. *The Journal of Pediatrics, 177*, 84–89. doi:10.1016/j.jpeds.2016.06.069

LeVay, S., Wiesel, T., & Hubel, D. (1980). The development of ocular dominance columns in normal and visually deprived monkeys. *Journal of Comparative Neurology, 191*(1), 1–51. doi:10.1002/cne.901910102

Leversen, K., Sommerfelt, K., Ronnestad, A., Kaaresen, P. I., Farstad, T., Skranes, J., . . . Markestad, T. (2011). Prediction of neurodevelopmental and sensory outcome at 5 years in Norwegian children born extremely preterm. *Pediatrics, 127*, e630–e638. doi:10.1542/peds.2010-1001

Levy, J., Hassan, F., Plegue, M., Sokoloff, M., Kushwaha, J., Chervin, R., . . . Shellhaas, R. (2017). Impact of hands-on care on infant sleep in the neonatal intensive care unit. *Pediatric Pulmonology, 52*(1), 84–90. doi:10.1002/ppul.23513

Liaw, J., Yang, L., Hua, Y., Chang, P., Teng, C., & Li, C. (2013). Preterm infants' biobehavioral responses to caregiving and positioning over hours in a neonatal unit in Taiwan. *Research in Nursing and Health, 35*(6), 634–646. doi:10.1002/nur.21499

Lickliter, R. (2011). The integrated development of sensory organization. *Clinics in Perinatology, 38*, 591–603. doi:10.1016/j.clp.2011.08.007

Liu, W., Laudert, S., Perkins, B., MacMillan-York, E., Martin, S., & Graven, S. (2007). The development of potentially better practices to support the neurodevelopment of infants in the NICU. *Journal of Perinatology, 27*, S48–S74. doi:10.1038/sj.jp.7211844

Mahmoodi, N., Arbabisarjou, A., Rezaeipoor, M., & Pishkar Mofrad, Z. (2015). Nurses' awareness of preterm neonates' sleep in the NICU. *Global Journal of Health Science, 8*(6), 226–233. doi:10.5539/gjhs.v8n6p226

Malcolm, W. (2015). NICU environment. *Beyond the NICU: Comprehensive care of the high-risk infant* (pp. 747–763). New York, NY: McGraw-Hill.

McGrath, J. M., Cone, S., & Samra, H. (2011). Neuroprotection in the preterm infant: Further understanding of the short- and long-term implications for brain development. *Newborn & Infant Nursing Reviews, 11*(3), 109–112. doi:10.1053/j.nainr.2011.07.002

McGregor, C. (2013). Big data in neonatal intensive care. *Computer, 46*(6), 54–59. doi:10.1109/MC.2013.157

Milford, C., & Zapalo, B. (2010). *The NICU experience and its relationship to sensory integration* (2nd ed.). Chicago, IL: National Association of Neonatal Nurses.

Moeskops, P., Benders, M. J., Kersbergen, K. J., Groenendaal, F., de Vries, L. S., Viergever, M. A., & Išgum, I. (2015). Development of cortical morphology evaluated with longitudinal MR brain images of preterm infants. *PLoS One, 10*, 1–22. doi:10.1371/journal.pone.0131552

Montirosso, R., Giusti, L., Prete, A., Zanini, R., Bellù, R., & Borgatti, R. (2016). Does quality of developmental care in NICUs affect health-related quality of life in 5-year-old children born preterm? *Pediatric Research, 80*(6), 824–828. doi:10.1038/pr.2016.158

Mony, K., Selvam, V., Diwakar, K., & Raghavan, V. R. (2018). Effect of nesting on sleep pattern among preterm infants admitted in NICU. *Biomedical Research, 29*(10), 1994–1997. doi:10.4066/biomedicalresearch.29-18-326

Moon, C. (2011). The role of early auditory development in attachment and communication. *Clinics in Perinatology, 38*, 657–669. doi:10.1016/j.clp.2011.08.009

Morag, I., & Ohlsson, A. (2016). Cycled light in the intensive care unit for preterm and low birth weight infants. *Cochrane Database of Systematic Reviews,* (8), CD006982. doi:10.1002/14651858.CD006982.pub4

Ortenstrand, A., Westrup, B., Brostrom, E., Sarman, I., Akerström, S., Brune, T., & Waldenström, U. (2010). The Stockholm neonatal family centered care study: Effects on length of stay and infant morbidity. *Pediatrics, 125*(2), e278–e285. doi:10.1542/peds.2009-1511

Papageorgiou, A., & Pelausa, E. (2014). Management and outcome of extremely low birth weight infants. *Journal of Pediatric and Neonatal Individualized Medicine, 3*(2), e030209. doi:10.7363/030209

Philben, M. K. (2004). Planning the acoustic environment of a neonatal intensive care unit. *Clinics in Perinatology, 31*, 331–352. doi:10.1016/j.clp.2004.04.014

Pickler, R. H., McGrath, J. M., Reyna, B., McCain, N., Lewis, M., Cone, S., . . . Best, A. (2010). A model of neurodevelopmental risk and protection for preterm infants. *Journal of Perinatal & Neonatal Nursing, 24*(4), 356–365. doi:10.1097/JPN.0b013e3181fb1e70

Pineda, R. G., Stransky, K. E., Rogers, C., Duncan, M. H., Smith, G. C., Neil, J., & Inder, T. E. (2012). The single patient room in the NICU: Maternal and family effects. *Journal of Perinatology, 32*, 545–551. doi:10.1038/jp.2011.144

Ranger, M., & Grunau, R. (2014). Early repetitive pain in preterm infants in relation to the developing brain. *Pain Management, 4*(1), 57–67. doi:10.2217/pmt.13.61

Rattaz, C., Goubet, N., & Bullinger, A. (2005). The calming effect of a familiar odor on full-term newborns. *Journal of Developmental Behavioral Pediatrics, 26*, 86–92. doi:10.1097/00004703-200504000-00003

Rea, M. S., & Figueiro, M. G. (2016). The NICU lighted environment. *Newborn & Infant Nursing Reviews, 16*(4), 195–202. doi:10.1053/j.nainr.2016.09.009

Rees, S., Harding, R., & Walker, D. (2011). The biological basis of injury and neuroprotection in the fetal and neonatal brain. *International Journal of Developmental Neuroscience, 29*(6), 551–563. doi:10.1016/j.ijdevneu.2011.04.004

Reynolds, L., Duncan, M., & Smith, G. (2013). Parental presence and holding in the neonatal intensive care unit and associations with early neurobehavior. *Journal of Perinatology, 33*, 636–641. doi:10.1038/jp.2013.4

Rivkees, S. A., Mayes, L., Jacobs, H., & Gross, I. (2004). Rest-activity patterns of premature infants are regulated by cycled lighting. *Pediatrics, 113*, 833–839. doi:10.1542/peds.113.4.833

Rodríguez, R., & Pattini, A. (2016). Neonatal intensive care unit lighting: Update and recommendations. *Archivos Argentinos de Pediatría, 114*(4), 361–367. doi:10.5546/aap.2016.eng.361

Sadatsafavi, H., Niknejad, B., Shepley, M., & Sadatsafavi, M. (2017). Probabilistic return-on-investment analysis of single-family versus open-bay rooms in neonatal intensive care units—Synthesis and evaluation of early evidence on nosocomial infections, length of stay, and direct cost of care. *Journal of Intensive Care Medicine, 34*(2), 115–125. doi:10.1177/0885066616689774

Saigal, S., & Doyle, L. (2008). An overview of mortality and sequelae of preterm birth from infancy to adulthood. *Lancet, 371*, 261–269. doi:10.1016/S0140-6736(08)60136-1

Sarnat, H., & Yu, W. (2015). Maturation and dysgenesis of the human olfactory bulb. *Brain Pathology, 26*, 301–318. doi:10.1111/bpa.12275

Schaal, B., Hummel, T., & Soussigan, R. (2004). Olfaction in the fetal and premature infant: Functional status and clinical implications. *Clinics in Perinatology, 31*, 261–285. doi:10.1016/j.clp.2004.04.003

Segers, E., Ockhuijsen, H., Baarendse, P., van Eerden, I., & van den Hoogen, A. (2019). The impact of family centred care interventions in a neonatal or paediatric intensive care unit on parents' satisfaction and length of stay: A systematic review. *Intensive & Critical Care Nursing*, *50*, 63–70. doi:10.1016/j.iccn.2018.08.008

Shahheidari, M., & Homer, C. (2012). Impact of the design of neonatal intensive care units on neonates, staff, and families: A systematic literature review. *Journal of Perinatal & Neonatal Nursing, 26*(3), 260–266. doi:10.1097/JPN.0b013e318261ca1d

Shepley, M. M., Smith, J. A., Sadler, B. L., & White, R. D. (2014). The business case for building better neonatal intensive care units. *Journal of Perinatology, 34*(11), 811–815. doi:10.1038/jp.2014.174

Shepley, M. M., Song, Y., & Marshall-Baker, A. (2016). Creating an environmentally sustainable neonatal intensive care unit. *Newborn and Infant Nursing Reviews, 16*(4), 213–237. doi:10.1053/j.nainr.2016.09.027

Stevens, D., Thompson, P., Helseth, C., Hsu, B., Khan, M., & Munson, D. (2014). A comparison of the direct cost of care in an open-bay and single-family room NICU. *Journal of Perinatology, 34*(11), 830–835. doi:10.1038/jp.2014.178

Striedter, G. F., Srinivasan, S., & Monuki, E. S. (2014). Cortical folding: When, where, how, and why? *Annual Review of Neuroscience, 38*, 291–307. doi:10.1146/annurev-neuro-071714-034128

Sullivan, R., & Toubas, P. (1998). Clinical usefulness of maternal odor in newborns: Soothing and feeding preparatory responses. *Biology of the Neonate, 74*, 402–408. doi:10.1159/000014061

Tarullo, A., Balsam, P., & Fifer, W. (2011). Sleep and infant learning. *Infant and Child Development, 20*, 35–46. doi:10.1002/icd.685

U.S. Green Building Council. (2009). *LEED reference guide for green building design and construction—Healthcare supplement*. Washington, DC: Author.

Valeri, B., Holsti, L., & Linhares, M. (2015). Neonatal pain and developmental outcomes in children born preterm. *Clinical Journal of Pain, 31*(4), 355–362. doi:10.1097/AJP.0000000000000114

Vohr, B. (2014). Speech and language outcomes of very preterm infants. *Seminars in Fetal & Neonatal Medicine, 19*(2), 78–83. doi:10.1016/j.siny.2013.10.007

Vohr, B., McGowan, E., McKinley, L., Tucker, R., Keszler, L., & Alksninis, B. (2017). Differential effects of the single-family room neonatal intensive care unit on 18- to 24-month Bayley scores of preterm infants. *Journal of Pediatrics, 185*, 42–48.e41. doi:10.1016/j.jpeds.2017.01.056

Wachman, E. M., & Lahav, A. (2011). The effects of noise on preterm infants in the NICU. *Archives of Disease in Childhood—Fetal and Neonatal Edition, 96*(4), F305–F309. doi:10.1136/adc.2009.182014

Welch, M., Stark, R., Grieve, P., Ludwig, R., Isler, J., Barone, J., & Myers, M. (2017). Family nurture intervention in preterm infants increases early development of cortical activity and independence of regional power trajectories. *Acta Pædiatrica, 106*(12), 1952–1960. doi:10.1111/apa.14050

White, R. D. (2004). Mothers' arms—The past and future locus of neonatal care? *Clinics in Perinatology, 31*(2), 383–387, ix. doi:10.1016/j.clp.2004.04.009

White, R. D. (2011). Designing environments for developmental care. *Clinics in Perinatology, 38*, 745–749. doi:10.1016/j.clp.2011.08.012

White, R. D. (2013). Recommended NICU design standards and the physical environment of the NICU. *Journal of Perinatology, 33*(Suppl. 1), S1. doi:10.1038/jp.2013.9

White, R. D. (2017). Circadian variation of breast milk components and implications for care. *Breastfeeding Medicine, 12*, 398–400. doi:10.1089/bfm.2017.0070

White, R. D. (2018). Defining the optimal sensory environment in the NICU: An elusive task. *Acta Pædiatrica, 107*(7), 1. doi:10.1111/apa.14296

White, R. D., Smith, J., & Shepley, M. (2013). Recommended standards for newborn ICU design, eighth edition. *Journal of Perinatology, 33*(Suppl. 1), S2–S16. doi:10.1038/jp.2013.10

Zores, C., Dufour, A., Pebayle, T., Dahan, I., Astruc, D., & Kuhn, P. (2018). Observational study found that even small variations in light can wake up very preterm infants in a neonatal intensive care unit. *Foundation Acta Pædiatrica, 107*, 1191–1197. doi:10.1111/apa.14261

CHAPTER 33

The NICU—Through a Mother's Eyes

Kelley Benham French and Leslie B. Altimier

INTRODUCTION

The birth of a baby is a milestone event for a family and is typically a joyous occasion. When a baby arrives much too early, or complications arise, and a neonatal intensive care unit (NICU) stay is required, this typically joyous occasion turns into a stressful, anxiety-filled nightmare for families. Parents are immediately separated from their newly born infant and, depending on the unit, it can take days, weeks, or months before they are "allowed" to hold and care for their new infant. Parents are frequently treated as visitors in the NICU, only able to visit their infant during certain times of the day and all the basic caregiving roles (e.g., changing diapers, taking temperatures) are fulfilled by nurses. Parents frequently feel like outsiders, that they don't fully understand what is going on, and that they are not included in decisions regarding their infant's health. Parents may experience feelings of disempowerment and doubt about their parenting abilities, which may lead to a lack of confidence, anxiety, and subsequent posttraumatic stress (Varghese, 2015). From these experiences, NICU parents have high levels of stress and anxiety, and frequently have trouble connecting with their new infant, leading to parental (mothers and fathers) psychological distress even 9 months postpartum (Carson, Redshaw, Gray, & Quigley, 2015).

Most NICUs claim to provide "family-centered care" or "family-integrated care"; yet, of the 100 NICUs that I consulted or toured for 20 years (from 1999 to 2019), over 80% had written family "visitation policies" that indeed stated the importance of the family, EXCEPT for during shift change, clinical rounds, procedures, admissions of other infants, and the list goes on.

Simply put, is this really family-centered care? A policy that includes the words "visitation" or "allowed" sends a clear message that the family are visitors and are not all that important, or as important as the NICU staff. NICU staff verbalize acceptance of families being involved in patient care, but their actions do not always reflect their words. Many units provide opportunities for parents to engage and provide care (or at a minimum, participate in care) of their hospitalized infant. However, these opportunities are sometimes offered to parents inconsistently based on the experience, confidence, and tenure of the nurses.

As caregivers, once we really listen to parents and their stories, we can begin to understand the parent experience and really support parents in the way they need support. To get honest and transparent feedback about different components of family-centered care, an author, professor, and, most importantly, parent (Kelley French) was asked a series of questions by Leslie Brinley Altimier, RN. Here are Kelley's stories illustrating her NICU experience through a mother's eyes.

1. ***Leslie Brinley Altimier (LBA), RN: Kelley, were you always welcomed by name and treated with courtesy and respect by the healthcare team staff? What actions by the healthcare team were welcoming, courteous, and demonstrated respect?***

   Kelley Benham French, (KBF) [Mother]: We were always made to feel like we mattered and that our presence was important to our baby. Everything—from the design of the unit, with private rooms and comfy chairs, to the obvious training and philosophy of the hospital staff—was designed to include us. Yet I really struggled in the beginning to feel like I could contribute. If not for the insistence of the nurses and nurse practitioner, I'm not sure I would have bonded in the NICU with our daughter like I did. I'm not sure if anyone used my name, especially at first, but that didn't bother me. Being called "Mom" was a new and thrilling experience that I cherished.

   I was blessed with a supportive and involved husband, and he was in a better place mentally to participate in the first few days. The nurses lavished attention and praise on him; I suppose it was because seeing a dad so involved was an anomaly, and probably because he baked them cookies. But, it did grate on me that he got so much attention when I could slip through the NICU in my rumpled pajamas practically unnoticed. It made me resent him for being the better parent. I often wondered if the staff would have treated us differently had we not been older, white, and middle class. I hope not. But, our advantages were clear. We had more support and resources than most of the other families, and we got a lot of attention from the nurses.

2. ***LBA: Did you always feel "listened" to? What are some things that the healthcare team did that made you feel they were listening and hearing what you were saying?***

   KBF: For the most part, I felt listened to, but less so when we had an unfamiliar nurse. We built trust and respect with our primary nurses over time, one long afternoon together after another. Still, we really struggled to know when to object or complain. For the most part, we are pleasers and we respect authority, and we frankly wanted the nurses to like us, because we firmly believed that if they liked us, they'd be

more responsive to our daughter. Again, there's a question of class here. If I'd been 17, homeless, or if I'd spoken another language, would anyone have taken my concerns seriously? I have no idea.

3. ***LBA: Is there an example of an action or comment that demonstrated staff were not really listening or hearing what you were saying?***

KBF: When we had a new nurse one day, several months into our stay, our daughter had an elevated temperature in the crib. The nurse requested a urine catheter culture to check for infection. I remembered the previous attempt to catheterize our baby and how she had screamed. I noted that our particular baby was difficult to "cath" and that she had been sleeping under a pile of blankets, which was unusual for her. I asked the nurse to hold off for half an hour, take away the blankets, and take her temperature again. The nurse pushed back, which seemed silly. It got tense, and I flatly refused to allow the catheter, and within a few minutes Juniper's temperature returned to normal.

Later, after discharge, Juniper had to be catheterized again, and I requested it be scheduled in conjunction with another procedure that required anesthesia. They had such a hard time with the catheter they had to call a urologist, who found scarring from the first NICU catheterization. Reflexively ordering a urine "cath" for a fever without thinking through other causes would have been unnecessary torture for my baby.

I'm not a medical expert, but what I can offer is continuity. I know if the routine has changed. I know what has worked in the past, and I know what has not worked. Continuity is the weak link in the NICU.

4. ***LBA: Do you feel that the healthcare team members could recognize parents' psychological challenges (anxiety, depression, frustration)?***

KBF: Some of the healthcare team seemed to be able to tell I was struggling. A note in our daughter's chart noted that "Mom is stressed." A very nice social worker checked in on us, but we were the least of her problems. So many families needed translation services, bus passes, a place to stay. We would never try to claim resources that should go to people who needed them more. And I would never add the burden of my mental health onto the already overloaded plates of the medical staff. I want them focused on my baby, not me.

A few weeks into our stay, I drove the 45 minutes across town to a counselor I used to see. I spewed my story and my anxiety at her for an hour and a half, and she could do little more than absorb it. I paid the $90 and drove back to the hospital. This counselor had helped me through some garden-variety stressors in my previous life, before my entire world turned inside out and all the things I used to care about fell away, to be replaced with only my tiny daughter and my overpowering terror and love. My therapist didn't know what NEC was, or what it felt like to pump 12 hours a day, or what a 1-lb baby feels like in your hands.

Surely, I thought, there are enough mothers in this hospital dealing with grief, anxiety, and PTSD to keep a whole unit of psychologists busy. Why not bring specially trained therapists right into the hospital, to the epicenter of the need?

5. ***LBA: What were the top three stressors/anxieties/frustrations you experienced as a parent in the NICU (Box 33.1)? Could something or someone have helped to decrease this stressor?***

KBF: Yes, I KNOW that anything can happen, I KNOW you don't have a crystal ball, and I KNOW that you're superstitious, but we made it 5 months before anyone suggested our daughter might live.

Pessimism

A little hope is okay too. Along with all the statistics about disability and death, what about some studies that help parents see how important their role is? What about some stats that validate how far we've already come?

We get a bunch of statistics on the first day, thanks to the NICHD neonatal outcomes estimator, but those odds were never updated as milestones passed. Most babies who die do so in the first week. How about a sit-down check-in after the first brain ultrasound with some new numbers and a new outlook? How about a sit-down check-in every 2 weeks? Every month? Every time a new doctor comes on scene?

The number of times a doctor sat down in a chair and talked to us in our 197 days in the NICU?

TWO.

Lack of Continuity

This was the hardest part of the whole experience. From day to day, our understanding of our baby's condition and forecast cascaded wildly depending on the perspective and tone of the nurse *du jour*.

After our baby took a turn for the better, a nurse gave us an extended lecture on all the ways she could still suffer and die. "Kids like her are scary kids," she told us, shaking her head. When she teetered on the brink, a doctor found a way to offer hope.

When we were with our primary care team, we learned to calibrate our expectations. We knew to ask harder questions of Dr. Sunshine and to take what Dr. Doom said with a grain of salt. That was a gift that experience brought us. Parents who don't have 6 months to adjust might not have the advantage of perspective that we developed.

When we had an unfamiliar doctor or nurse, we could not read the tea leaves, and were nearly as lost as we had been on our first day. We held our breath for days until our primary nurse returned. We prayed our primary nurse practitioner would return from vacation. Nights and weekends were hell.

We understood that everyone needed time off, and that keeping the staff rested was good for everyone, including our daughter. But our 1-lb baby didn't understand day or night, and her body did not respect vacation schedules. Why should the staffing be thinner after dark? Why should we have to deal with a whole new team on the weekend? This would not be such an issue over on the feeder-and-grower side of the NICU, but on the critical side in our tertiary care center, it was a huge issue for us.

Jargon

I teach and study language, but I've never felt the power of language as acutely as I did in the NICU. Every profession has its jargon, its code, and medicine is no exception. Jargon makes us feel like part of a tribe. And people who work in high-stress environments especially need to feel the support and camaraderie of the tribe.

Box 33.1

TOP THREE STRESSORS/ANXIETIES/FRUSTRATIONS PARENTS EXPERIENCED IN THE NICU

1. Pessimism
2. Lack of continuity
3. Medical jargon

But the problem with jargon in the NICU is that it sends an equally powerful message to newcomers. New parents—dazed, disoriented, depressed, sleep-deprived—are already baffled by the foreign landscape of machinery and the metric system. So, when the humans in the room speak about morbidities and trials of life, the gulf between the parent and child yawns wider.

How can a parent feel close to a baby encased in plexiglas, ensnared by wires, and guarded by uniformed people who speak in code? When a neonatologist said our daughter was likely to develop a number of "morbidities," I didn't know that could mean anything as mild as nearsightedness, because the word "morbid," for nonscientists, conjures all sorts of gruesome imagery. All I saw were coffins.

When he asked, "Do you want everything done?" I had no understanding of what he meant by "everything." I pictured cracking her ribs during futile CPR.

I met a father this year who, 2 years after the death of his son, was still angry to the point of tears over the phrase "incompatible with life." In his fear and grief, he simply could not process what the term meant.

The people who made us feel steady on our feet used words that can be hard to say and hard to hear, but whose meaning was clear. Death. Die. Disabled. Blind.

Jargon offers us an emotional shield. It distances us from the things that are hard to say and feel. But, in the NICU, what parents need is someone who can speak across the divide.

6. ***LBA: What made you feel most like a mom to your baby and who had an impact on you feeling like a mom/dad to your baby?***

KBF: Nurses! When I met my daughter, I was afraid. I was afraid that she'd be so alien and incomplete that I wouldn't recognize her. I was afraid that I'd love her, and that would only make losing her harder. I had convinced myself that God, or the universe, or whoever, was punishing me for defying nature in conceiving her through IVF. I had convinced myself that God wouldn't kill her unless I was there to watch. If I stayed away, she would be safe. None of those feelings was rational, but who is rational at such a time?

It started with a little bow on our baby's head. A tiny thing, but it did send a message. This is your daughter. Get to know her.

7. ***LBA: What would be the most valuable feedback you could give a nurse or doctor to help them support parents in feeling more like a real "mom or dad"?***

KBF: I teach storytelling. A story needs a central character, and the most important quality of that character is that they have power over their situation. That's why Sleeping Beauty sucks and Moana is amazing.

A parent feels like he or she has no power. Imagine being trapped in the most important story of your life, watching your baby die, and being powerless to help. Imagine that your baby is dead, and all you did was watch. Why wouldn't you run?

Without those nurses, would I have become one of those parents who disappeared? I would not have stopped coming entirely, but I might have said I had to work, or pump, or come up with a million excuses not to engage. It's easy to look around the NICU and see the empty chairs and judge the parents who are not there. I don't judge them anymore. I could have been one of them. I was carrying an impossible amount of guilt over my body ejecting my daughter at 23 weeks. I couldn't hold her, couldn't feed her, couldn't do any of the things that mothers are supposed to do.

I conceived with an egg donor, so I didn't even share her DNA. When I signed consent forms, I wrote "Mom" next to my name. But in what way was I her mother? I became her mother, truly, thanks to the actions and the insistence of the NICU nurses.

8. ***LBA: When and how did you first touch your baby in the NICU?***

KBF: The first time I held her was a Tuesday, and on Tuesdays they clean the incubators. So, while they had the baby out, why not hold her? She was 2 weeks old.

Later, we would learn that a young nurse named Courtney talked the doctor into allowing it because she'd recently trained in developmental care. The doctor allowed it because she thought the baby would die anyway, and every mom should hold their baby once while it is still alive. It seems like simple compassion, letting a baby and a mom be together. But we know this is actually a crucial moment. Clinically, this is what she needed. She breathed better and held her temperature better when she was skin to skin.

But the moment might have been even more important in my life. Even when babies do die, the doctors and nurses are helping the parents write the story of their short lives, and of our lives as their parents. The story has to be one that we can live with for the rest of our lives. It might be the only story we will ever have of who we were in that moment and how we formed a family.

My daughter lived. And now, the nurses and family and even strangers like to tell my husband and me that she lived in part because we were such great parents to her. Because we were there for her, reading, singing, and holding her hand. Some of that is true. But I could not have been that parent without those nurses.

People say, "She's a miracle." I believe that's true. But as my friend Stephen told me, "Love is the miracle." The miracle was that those nurses loved her, and they made me feel safe enough that I could love her too.

9. ***LBA: Did the healthcare team encourage you to participate and take over parts of your baby's care?***

KBF: Nurses pulled me out of my fog and told me to put my hands into the incubator and touch her. I am certain that if the nurses had not forced me to engage, my daughter would not be alive.

- Here. Change her diaper.
- Here. Swab her mouth.
- Here. Lift her so I can weigh her.

10. ***LBA: Is there an example of something a healthcare team member said or did that discouraged you from participating in the care of your baby?***

KBF: Once, when our baby swelled beyond recognition and began to leak fluid through her pores, the medical team was stumped at how to make it stop. I blurted out something at rounds that probably felt absurd to the medical team. "When my iPhone gets wet, everyone tells me to put it in a bag of rice," I said. "Should we set the baby on a bag of rice?" Someone smiled condescendingly, and I was embarrassed and that was the end of it. That nonverbal "look" discouraged me from speaking up. It sounds dumb even as I type it. But there has always been a little part of my brain that has nagged at me asking, "*What would it have hurt?*"

11. ***LBA: Did you provide input during multidisciplinary daily rounds on your baby?***

    KBF: We always tried to be there for rounds, because often our observations didn't mesh with whatever had been charted or documented, or with the recollections or understanding of the team that rounded 12 hours or 3 days later. Details get lost over time. When did that darkness on her belly first appear? Did her head swell first or her chest? What percentage of the time does she recover from a drop in her saturations on her own? Those are the kinds of details that we seemed to hold on to.

    Only once during rounds did a doctor ever ask us what we thought. When it happened, it came as a shock. Why was the doctor asking us? Why was everyone looking at us now? But, in retrospect, we should have been asked more often. We **DID** have something to contribute.

12. ***LBA: Did you consistently attend nurse hand-offs/shift changes while your baby was in the NICU?***

    KBF: We were not allowed to be present at shift change, and I never understood why. I think it had to do with HIPPA and possibly overhearing something being discussed nearby about another patient.

13. ***LBA: Did you complete any "charting/documentation" of your baby's activities, feedings, output, etc.?***

    KBF: We were never asked to chart or document, although we would have liked to have some input, especially when our assessment and/or views did not mesh with what had been stated or documented.

14. ***LBA: Did you consistently read the healthcare team's documentation (in the EMR) about your baby's conditions, results, and care?***

    KBF: I tried to read the chart once, but was told that if I wanted to do so I needed to make an appointment to do it with a doctor present, so the doctor could explain anything confusing. I understand the reason for that policy, but I didn't like it, and I never asked again.

    After discharge, I ordered the entire 7,000-page chart, and I saw many things I hadn't known at the time and things that I would have liked the opportunity to clarify or expand on in the moment. I also saw a general over-focus on detail and a lack of synthesis or attitude. Detail matters, but so does the narrative, the arc. The charting system did not seem to leave space for meaning.

15. ***LBA: Did you feel prepared and ready for the discharge of your baby from the NICU?***

    KBF: You might think that after 197 days, we'd feel prepared for discharge. But we were terrified. I cried.

    What would I do without the nurses who had held my hand, translated for me, supported me? What would my daughter do without the people who knew how to get her to eat, calm her cries, settle her to sleep?

    When my husband and I walked her out of the hospital, our primary nurse, Tracy, walked beside us. "She's not going to know which one of us is her mother until we get to the car," I said. I was not kidding.

    My daughter had heard Tracy's voice from her first days, had felt Tracy's hands, smelled Tracy's smell. Tracy had played her favorite music for her when we weren't around, had changed the batteries on her mobile, and kept her in fashionable outfits and fancy homemade hats. Thanks to Tracy, the love our daughter had known had been multiplied. So, when we walked out, the car seat bumping against my knee, it felt wrong—cruel even—to leave Tracy behind. She never treated our daughter like a patient, only like a little girl.

16. ***LBA: What were your biggest "aha" moments in the years after your baby was discharged that could have been* stressed *more during the NICU stay, or could have prepared you more for your baby's future?***

    KBF: I wish someone had told me that:

    - There's so much more hope in the research;
    - Babies with involved parents have as big an advantage as not getting a brain bleed;
    - I mattered, and that the idea that I mattered was supported by science. These studies do exist, so why share statistics about nearsightedness, but not share statistics about parental engagement?
    - It would be terrifying, yes, but
    - It would also be exhilarating, fascinating, boring, funny, and transformative, and that when it was over, I would not give up that time in my life—I would not go back to the person I had been before—for anything in the world.
    - Before she was born, when we were asked to decide whether to "do everything" to save her or let her die at birth, I wish someone had told me that I was trying to make a decision as a person I had not yet become. The things that mattered to me in that moment were not the same things that would matter to me 6 months later.
    - It was OK to be afraid (Box 33.2).

    There are studies on this too, though. People who come out the other side of these things with disabilities rate their quality of life pretty high.

    - Our daughter came home on no oxygen, no monitors, and no meds of any kind.

    By some standards, though, she was an "unfavorable outcome." She battled NEC, ROP, CLD—so many acronyms that statisticians and researchers used to measure outcomes. But, every one of those "morbidities" resolved on its own before discharge.

    - She came home. She rolled over, sat up, walked, talked, sang, ran.
    - She dances. She reads. She rides horses. She writes songs for her little sisters.

    Every day in the NICU, there is suffering, there are heartaches, and there are goodbyes. Those stories surely weigh on the hearts and consciences of the nurses and doctors who knew, loved, and lost those kids. But, every day there is also invention, surprise, and wonder. And, so many kids thrive after discharge in so many astonishing and ordinary ways. They sell Girl Scout cookies, climb trees, dance in the Nutcracker,

Box 33.2

WE WERE AFRAID

- Of disability
- That we were too old
- That we couldn't handle it
- That our daughter would hate her life, and that she would blame us

swim in the deep end, and read their first chapter books. They don't visit the NICU nearly often enough, but their successes are still your successes. So, as you guard against the terrible things that can happen, I challenge you to kick out a window for hope. For the things you can't see and wouldn't predict. Because those stories are happening every day, too. And the lessons of those stories are just as important as the harder ones, probably more.

17. ***LBA: Kelley, thank you so much for your open and transparent discussion about the NICU experience through your eyes—a mom's eyes.***

    As NICUs strive to create partnerships with parents and families, we need to move from words and theories to actions and reality. Building family partnerships begins with trust from all involved. To build a trusting relationship, difficult questions need to be asked and answered in an open and transparent just culture. Understanding needs and wants from a family's perspective can only be met by listening: listening to parents and meeting their needs at their level of understanding. We cannot assume that every parent wants the same information, which is why listening and asking about their needs and wants is vitally important.

References related to the content of the questions asked of Kelley are listed in the text that follows.

To find out more about the family experience through a mother and father's set of eyes, I ask you to join me in reading an amazing book by both Kelley Benham French and her husband, Thomas French (2016). Kelley and Thomas French chose to fight for their daughter, Juniper's life, and this is their incredible tale.

> Juniper French was born 4 months early, at 23 weeks' gestation. She weighed 1 lb, 4 ounces, and her twiggy body was the length of a Barbie doll. Her head was smaller than a tennis ball, her skin was nearly translucent, and through her chest you could see her flickering heart. Premature babies like Juniper, born at the edge of viability, trigger the question, "Which is the greater act of love—to save her, or to let her go?" Kelley and Thomas French chose to fight for Juniper's life, and this is their tale. In one memoir, the authors explore the border between what is possible and what is right. They marvel at the science that conceived and sustained their daughter and the love that made the difference. They probe the bond between a mother and a baby, between a husband and a wife. They trace the journey of their family from its fragile beginning to the miraculous survival of their now thriving daughter.

RECOMMENDED READINGS

Abdel-Latif, M., Boswell, D., Broom, M., Smith, J., & Davis, D. (2015). Parental presence on neonatal intensive care unit clinical bedside rounds: Randomised trial and focus group discussion. *Archives of Disease in Childhood, 100*(3), F203–F209. doi:10.1136/archdischild-2014-306724

Altimier, L., & Phillips, R. (2016). The neonatal integrative developmental care model: Advanced clinical applications of the seven core measures for neuroprotective family-centered developmental care. *Newborn and Infant Nursing Reviews, 16*(4), 230–244. doi:10.1053/j.nainr.2016.09.030

Axelin, A., Outinen, J., Lainema, K., Lehtonen, L., & Franck, L. (2018). Neonatologists can impede or support parents' participation in decision-making during medical rounds in neonatal intensive care units. *Acta Pediatrica, 107*(12), 2100–2108. doi:10.1111/apa.14386

Bigani, D., & Correia, A. (2018). On the same page: Nurse, patient, and family perceptions of change-of-shift bedside report. *Journal of Pediatric Nursing, 41*, 84–89. doi:10.1016/j.pedn.2018.02.008

Bucknall, T., Hutchinson, A., Botti, M., McTier, L., Rawson, H., Hewitt, N., . . . Chaboyer, W. (2016). Engaging patients and families in communication across transitions of care: An integrative review protocol. *Journal of Advanced Nursing, 72*(7), 1689–1700. doi:10.1111/jan.12953

Chung, R., Kim, U., & Basir, M. (2018). Differing perspectives on parent access to their child's electronic medical record during neonatal intensive care hospitalization: A pilot study. *The Journal of Maternal-Fetal and Neonatal Medicine, 31*(8), 1078–1084. doi:10.1080/14767058.2017.1306853

Dittman, K., & Hughes, S. (2018). Increased nursing participation in multidisciplinary rounds to enhance communication, patient safety, and parent satisfaction. *Critical Care Nursing Clinics of North America, 30*(4), 445–455.e4. doi:10.1016/j.cnc.2018.07.002

Friesen, M. A. (2013). Developing a patient-centered ISHAPED handoff with patient/family and parent advisory councils. *Journal of Nursing Care Quality, 28*(3), 208–216. doi:10.1097/NCQ.0b013e31828b8c9c

Griffin, T. (2010). Bringing change-of-shift report to the bedside: A patient- and family-centered approach. *The Journal of Perinatal & Neonatal Nursing, 24*(4), 348–353. doi:10.1097/JPN.0b013e3181f8a6c8

Gustafson, K., LaBrecque, M., Graham, D., Tella, N., & Curley, M. (2016). Effect of parent presence during multidisciplinary rounds on NICU-related parental stress. *Journal of Obstetric, Gynecologic, and Neonatal Nursing, 45*(5), 661–670. doi:10.1016/j.jogn.2016.04.012

Hynan, M. T., Steinberg, Z., Baker, L., Cicco, R., Geller, P. A., Lassen, S., . . . Stuebe, A. (2015). Recommendations for mental health professionals in the NICU. *Journal of Perinatology, 35*(Suppl. 1), S14–S18. doi:10.1038/jp.2015.144

Institute of Medicine. (2001). *Crossing the quality chasm: A new health system for the 21st century* (Report). Washington, DC: National Academies Press. Retrieved from http://www.nap.edu/html/quality_chasm/reportbrief.pdf

Kim, H. (2018). Social support provision: Perspective of fathers with preterm infants. *Journal of Pediatric Nursing, 39*, 44–48. doi:10.1016/j.pedn.2018.01.017

Lee, S., & O'Brien, K. (2014). Parents as primary caregivers in the neonatal intensive care unit. *Canadian Medical Association Journal, 186*(11), 845–847. doi:10.1503/cmaj.130818

Lee, S., & O'Brien, K. (2018). Family integrated care: Changing the NICU culture to improve whole-family health. *Journal of Neonatal Nursing, 24*(1), 1–3. doi:10.1016/j.jnn.2017.11.003

Nuss, T., Kelly, K., Campbell, K., Pierce, C., Entzminger, J., Blair, B., . . . Walker, J. (2014). The impact of opening visitation access on patient and family experience. *Journal of Nursing Administration, 44*(7/8), 403–410. doi:10.1097/NNA.0000000000000090

O'Brien, K., Robson, K., Bracht, M., Cruz, M., Lui, K., Alvaro, R., . . . Dow, K. (2018). Effectiveness of family integrated care in neonatal intensive care units on infant and parent outcomes: A multicentre, multinational, cluster-randomised controlled trial. *The Lancet Child & Adolescent Health, 2*(4), 245–254. doi:10.1016/S2352-4642(18)30039-7

Palma, J. P., Keller, H., Godin, M., Wayman, K., Cohen, R. S., Rhine, W. D., & Longhurst, C. A. (2012). Impact of an EMR-based daily patient update letter on communication and parent engagement in a neonatal intensive care unit. *Journal of Participatory Medicine, 4*, e33. Retrieved from https://link.ezproxy.neu.edu/login?url=http://search.ebscohost.com/login.aspx?direct=true&db=cmedm&AN=23730532&site=ehost-live&scope=site

Pineda, R., Bender, J., Hall, B., Shabosky, L., Annecca, A., & Smith, J. (2018). Parent participation in the neonatal intensive care unit: Predictors and relationships to neurobehavior and developmental outcomes. *Early Human Development, 117*, 32–38. doi:10.1016/j.earlhumdev.2017.12.008

Sedlock, E., Ottosen, M., Nether, K., Sittig, D., Etchegaray, J., Tomoaia -Cotisel, A., ... Thomas, E. (2018). Creating a comprehensive, unit-based approach to detecting and preventing harm in the neonatal intensive care unit. *Clinical Risk, 23*(4), 167–175. doi:10.1177/2516043518787620

Shandra Bos, L., Shorey, S., Kulantaipian, T., Sng, J., Tam, W., & Koh, S. (2018). Effectiveness of the neonatal discharge program for very low-birth-weight infants on parental efficacy and psychological distress. *Journal of Perinatal and Neonatal Nursing, 32*(4), E11–E21. doi:10.1097/JPN.0000000000000337

Smith, L., & Carver, A. (2017). Improving patient safety through daily multidisciplinary rounds. *Journal of Obstetric, Gynecologic, and Neonatal Nursing, 46*(3 Suppl.), S41–S42. doi:10.1016/j.jogn.2017.04.109

Sorra, J., Famolaro, T., Dyer, N., Nelson, D., & Smith, S. A. (2012). *Hospital survey on patient safety culture: 2012 user comparative database report* [AHRQ publication no. 12-0017]. Retrieved from https://www.ahrq.gov/sites/default/files/wysiwyg/professionals/quality-patient-safety/patientsafetyculture/hospital/2012/hospsurv121.pdf

Tandberg, B., Frøslie, K., Flacking, R., Grundt, H., Lehtonen, L., & Moen, A. (2018). Parent-infant closeness, parents' participation, and nursing support in single-family room and open bay NICUs. *Journal of Perinatal and Neonatal Nursing, 32*(4), E22–E32. doi:10.1097/JPN.0000000000000359

The Joint Commission for Transforming Healthcare. (2013). *Facts about the hand-off communications project*. Retrieved from https://www.jointcommission.org/mobile/standards_information/national_patient_safety_goals.aspx

The Joint Commission. (2012). *2011–2012 national patient safety goals*. Retrieved from https://www.jointcommission.org/mobile/standards_information/national_patient_safety_goals.aspx

Tidwell, T., Edwards, J., Snider, E., Lindsey, C., Reed, A., Scroggins, I., . . . Brigance, J. (2011). A nursing pilot study on bedside reporting to promote best practice and patient/family-centered care. *Journal of Neuroscience Nursing, 43*(4), E1–E5. doi:10.1097/JNN.0b013e3182212a1d

Tubbs-Cooley, H. L., Mara, C. A., Carle, A. C., Mark, B. A., & Pickler, R. H. (2019). Association of nurse workload with missed nursing care in the neonatal intensive care unit. *Journal of the American Medical Association Pediatrics, 2019, 173*(1), 44–51. doi:10.1001/jamapediatrics.2018.3619

Tubbs-Cooley, H., Pickler, R., Younger, J., & Mark, B. (2015). A descriptive study of nurse-reported missed care in neonatal intensive care units. *Journal of Advanced Nursing, 71*(4), 813–824. doi:10.1111/jan.12578

Voos, K., & Park, N. (2014). Implementing an open unit policy in a neonatal intensive care unit: Nurses' and parents' perceptions. *Journal of Perinatal and Neonatal Nursing, 28*(4), 313–318. doi:10.1097/JPN.0000000000000055

REFERENCES

Carson, C., Redshaw, M., Gray, R., & Quigley, M. A. (2015). Risk of psychological distress in parents of preterm children in the first year: Evidence from the UK Millennium Cohort Study. *BMJ Open, 5*(12), e007942.

Varghese, M. (2015). A study on parental stress in the neonatal ICU using parental stressor. *Pediatrics, 135*(Suppl. 1), S9. doi:10.1542/peds.2014-3330O

French, K. B., & French, T. (2016). *Juniper: The girl who was born too soon.* Boston, MA: Little, Brown and Company.

CHAPTER 34

Touch a Life, Impact a Lifetime: Trauma-Informed Care in the NICU

Mary E. Couglin McNeil and Amy D'Agata

INTRODUCTION

The scenario in Exhibit 34.1 is fictitious, yet events like this happen far too often and change the course of a family's pregnancy expectations and their lives forever. As we know, maternal and/or fetal complications affect about 10% of births in the United States (Harrison & Goodman, 2015). When complications occur, families are typically grateful for the advancing technology available in neonatal intensive care units (NICU); however, admission to the NICU is rarely a benign event. One unintended consequence of NICU care is the pervasive suffering experienced by the infant, the family, and the clinicians (D'Agata, Coughlin, & Sanders, 2018). In this chapter, we uncover the suffering of infants, parents, and clinicians, which will provide the framework for why NICU practice is ripe for a paradigm shift. A shift that acknowledges the traumatic nature of NICU care, both for care recipients and care practitioners, and actively seeks to reduce the experience of toxic stress and mitigate the associated trauma. We also provide tools

EXHIBIT 34.1

HIGH SCHOOL GRADUATION!

Tracy, Shannon, and Erin are NICU nurses at Elmwood Medical Center. Seventeen years ago, they were part of the team of nurses who cared for Katie Walsh. Katie was memorable to these nurses for several reasons. First, the circumstances of her birth were tragic. Second, her family has maintained contact with the NICU by visiting each year around Katie's birthday. Finally, for years the NICU team has supported Katie's interest to one day herself become a NICU nurse. Next week, Katie will graduate high school and many of her former nurses will be at her graduation party. In the fall, Katie will be attending college in Pennsylvania as a nursing major, just like her mom. This accomplishment is relished by all who know Katie because of the many hurdles she has faced.

Since Katie entered elementary school, her former nurses have been aware of Katie's learning and sensory processing challenges. Her sensory processing issues cause her to be sensitive to noise and touch. Early on, Katie was diagnosed with attention deficit and executive function disorders. Katie received individualized educational support for the last 10 years to help ensure her academic success.

Most recently, Katie has shared with the nurses her struggles with anxiety and depression. Katie was diagnosed last year with major depressive disorder. Following her most recent crisis, Katie tried to describe to Tracy, Shannon, and Erin the storm of emotions that flood her mind during an "event," as she calls it. Katie not only suffers mentally when a crisis occurs but also physically, so much so that some days she cannot get out of bed because of the pain she feels. Katie says the treatment she has been receiving for her depression has been really helpful, and it has been 6 months since her last "event."

Katie learned the circumstances of her birth at an early age. Her family shared that she was born at 23 weeks' gestation following her mother's brain aneurysm, an event that her mom did not survive. As Katie was growing up, her dad and grandparents surrounded her with love and made sure she received all the help possible to overcome being born so early. In fact, as far back as she can remember, her teachers and therapists have told her that many of her challenges are probably linked to her premature birth. They have explained that lots of painful procedures are done to premature babies during the weeks and months they are in the hospital, and that these experiences can affect how the brain develops.

Tracy, Shannon, and Erin are excited to share in Katie's graduation celebration. They feel proud to have been part of her life since birth. Over the years, the nurses have talked together about Katie's challenges. They know premature birth increases the risk for suboptimal outcomes, yet have wondered to what extent their care may have played a role in Katie's outcomes. Fortunately, Katie escaped major complications, but they have seen the toll her learning, sensory, and mental health issues have taken on Katie, her dad, and her grandparents. The nurses wonder if there are practice changes they could make to decrease the risk for outcomes like these.

Clinician Questions:

1. *How does this scenario make you feel?*
2. *Have you cared for infants and families that you have maintained a relationship with beyond the NICU?*
3. *Do you ever wonder how the care you provide affects infants?*

EXHIBIT 34.2

KATIE WALSH'S PRETERM BIRTH

Jake and Kimberly Walsh met in college. Jake was from Seattle and Kimberly from a small town outside of Atlanta. They met during an undergraduate English class and discovered they both had a love of running. After graduating from college and completing their first marathon, they both began their careers in Philadelphia, Jake as a middle school teacher and Kimberly as a staff nurse in the cardiac ICU of a trauma center. They were very much in love and began planning their wedding and life together. They were married 4 years after finishing college and found out they were pregnant with their first baby 1 year later. At the age of 27, they were both the epitome of health and thrilled about their uneventful pregnancy.

At 23 weeks, Kimberly continued working 12-hour shifts and picking up extra shifts here and there. After finishing her week, Kimberly was looking forward to her 4-day weekend with Jake. On Friday morning, Kimberly began her day at yoga, stopped for brunch with her best friend, and then went grocery shopping before heading home. Once at home, she put the groceries away and started a load of laundry when she noticed a headache coming on. Kimberly decided she would rest on the sofa before Jake arrived home in half an hour. Her headache quickly changed from tolerable to blinding in minutes.

Kimberly began sweating and sensed she was going to vomit. She made her way to the bathroom, which is where Jake found her moments later. Kimberly was barely responsive and Jake immediately called 911. He cradled his wife and told her over and over again everything was going to be okay, help was on the way for her and the baby. By the time emergency medical services arrived, Kimberly had become unresponsive and was intubated on the bathroom floor. In the emergency room, Jake was told the horrific news that it appeared Kimberly may have suffered a brain aneurysm; her condition was grave and the baby needed to be delivered immediately.

Kimberly was transported to the main operating room. Due to the urgency of the situation, Jake was not allowed to attend the birth. A labor and delivery nurse escorted Jake to the waiting area and remained with him. When the surgery was complete, the surgeon congratulated Jake on the birth of his baby girl. The baby had been stabilized and transferred to the NICU. His wife, Kimberly, had suffered a massive brain aneurysm. The surgeons tried desperately to save her but were unable.

for how clinicians can begin to incorporate trauma-informed care into their practice. First, let us look back at the events that resulted in Katie Walsh's preterm birth (Exhibit 34.2).

WHY DID YOU CHOOSE TO PRACTICE IN THE NICU?

We all choose to practice in the NICU for different reasons; however, often a common denominator is a desire to make a difference in the lives of vulnerable newborns and their families. Despite the difficulties NICU clinicians face in their day-to-day role responsibilities, compassion and the desire to help others are typically what drive our commitment to this fragile patient population. In an effort to develop trust and partnership between the healthcare team and families, clinicians work hard to create relationships with parents and families. As demonstrated in the opening scenario, a strong bond was developed in the NICU between the nurses and Katie's family. Therapeutic relationships are a cornerstone of nursing, deepening our connection with the people we serve and providing us with insights that enhance our ability to meet their needs. However we must be aware that bearing witness to the suffering of others may come at a cost; stories like the Walshs', and those of every family we care for, affect us deeply.

For years, NICU clinicians have primarily viewed the importance of their role and their impact on outcomes specifically related to the neonatal period. Our focus has been the provision of life-sustaining care, birth to discharge. Ideally, the NICU team is present at delivery to provide life-saving care and then infants are transferred to the NICU for ongoing care until discharge. Given the increasing rates of survival reported, neonatal medicine is succeeding with this goal. While medicine continues to fine-tune treatment protocols, attention now must pivot toward improving *quality* of life for those infants who survive the NICU (Exhibit 34.3). Care provided by NICU nurses requires awareness that every care encounter has implications not just in the moment of care, but also for the developmental trajectory of the infant–family dyad across the life span (Shonkoff et al., 2012).

Intensive care nursing is challenging on many fronts to include competing priorities, complex patient assignments and a myriad of mission critical tasks. A focus on the psycho-socio-emotional dimensions of NICU nursing often takes a back seat to life-saving care for the infant. Accordingly, as we care for multiple patients, our work can become very task-oriented and we can inadvertently lose sight of the bigger picture. For many of us, this is through no fault of our own as we were never trained to understand just how critical our immediate actions may be to future outcomes. We were trained to be focused in the moment to be able to recognize and anticipate clinical complications and plan for proper, immediate treatment interventions.

As to the lack of nursing training, we are not suggesting ill intent. Rather, neonatology is a medical specialty in its own infancy, and as the specialty grows, we all need to broaden our focus to include quality care measures that support infant brain development and social–emotional health. To do so, we need a common understanding of the infant experience, and that of the family and clinician.

WHAT IS TRAUMA?

Trauma has traditionally been a word to describe physical injuries or wounds. During the 19th century, *trauma* evolved to include psychological phenomenon. The Substance Abuse and Mental Health Services Administration (SAMHSA) of the United States defines individual trauma as the result of "an event, series of events, or set of circumstances that is experienced as physically or emotionally harmful or life threatening and that has lasting adverse effects on the individual's functioning and mental, physical, social, emotional, or spiritual well-being" (SAMHSA, 2014). The current symptomatology of trauma includes intrusive re-experiencing, avoidance behavior, alterations in cognition and mood, and hyperarousal (American Psychiatric Association, 2013).

EXHIBIT 34.3

KATIE'S CARE IN THE NICU

As soon as Katie was delivered from her mother, the blue and limp baby was placed on a warmer and the NICU team began providing neonatal resuscitation. She was quickly placed into a thermoregulation bag, suctioned orally and nasally five times, successfully intubated on the third attempt, and an umbilical line was placed. Once stabilized, the baby was transported from the main OR to the NICU, which was several long corridors and five floors away. During the transport, a nurse manually bagged the baby while navigating the transport isolette and monitoring vital signs.

During the course of Katie's care in the NICU, she was intubated and extubated several times, experienced a number of feeding intolerance episodes, "NEC scares," and sepsis. Katie was eventually discharged from the NICU at 39 weeks into the care of her father.

Information about Katie's course of NICU care was captured using the Neonatal Infant Stessor Scale (NISS), see Box 34.1. The NISS allows clinicians to see the quantity of painful and stressful interventions infants have experienced during care. Data are organized into categories of intensity: *extremely stressful*, *very stressful*, *moderately stressful,* and *a little stressful*.

The following are the weekly quantities of pain and stress events Katie experienced in the first 4 weeks of life:

	Katie's Total
Week 1	345
Week 2	483
Week 3	396
Week 4	409

According to data collected in the first 4 weeks of life, Katie's extremely preterm brain was exposed to **1,633** stressful events. This exposure is in contrast with a healthy term infant who typically is suctioned multiple times at delivery, receives a couple of injections, and has heelsticks for newborn screening. Comparing these pain and stress exposures, Katie experienced almost **200 times** the number of adverse exposures in just the first month of life, as compared to a healthy term infant.

Box 34.1

NEONATAL INFANT STRESSOR SCALE

The Neonatal Infant Stressor Scale instrument categorizes interventions and procedures according to clinician-assumed severity of pain or stress. The categories are *extremely stressful, very stressful, moderately stressful,* and *a little stressful.* Examples of interventions included in each category are as follows:

- *Extremely stressful:* multiple IV, intra-arterial, and umbilical venous catheter/umbilical arterial catheter attempts, intubation, chest tube insertion, eye examination
- *Very stressful:* nasal, oral, and endotracheal tube suctioning, heelsticks, single IV insertion, lumbar puncture
- *Moderately stressful:* diaper change, position change, gavage feeding, x-ray, receiving continuous positive airway pressure
- *A little stressful:* mouth care, IV flushing, stomach aspiration via nasogastric tube, application of body cream

IV, intravenous.

Source: From Newnham, C. A., Inder, T. E., & Milgrom, J. (2009). Measuring preterm cumulative stressors within the NICU: The neonatal infant stressor scale. *Early Human Development, 85*(9), 549–555. doi:10.1016/j.earlhumdev.2009.05.002

Within the context of the NICU, trauma has been recognized for years as a critical psychological experience. Interestingly though, this traumatic experience has primarily been described from the parental perspective, and not the infant or clinician's perspective (Lasiuk, Comeau, & Newburn-Cook, 2013; Lefkowitz, Baxt, & Evans, 2010). Our intention is not to compare severity of experience, as many parents suffer greatly from their experience of premature birth and separation from their baby. Rather, we believe it is critically important to also include the infant experience into these discussions, the individual to whom direct physical trauma and social–emotional trauma may occur as a result of his or her medical experience. Acknowledging that NICU clinicians may also be traumatized by their burden of care experience is very important. Caregivers, albeit parents and/or clinicians, cannot provide high-quality, empathetic care when they themselves are suffering under the weight of unresolved trauma exposure.

Infants

Infants of all gestational ages requiring NICU care are potentially vulnerable to a traumatic experience. The degree of prematurity or illness at birth, due to the duration of medical care and frequency of interventions, may indicate the most vulnerable infants. While there are some factors critically important to infant development that are beyond the control of NICU clinicians (e.g., prenatal factors, birth immaturity, and state of health or illness), protective opportunities exist in other areas. The risk factors of NICU care are the basis of the *Infant Medical Trauma in the NICU* (IMTN) conceptual model, Figure 34.1 (D'Agata, Young, Cong, Grasso, & McGrath, 2016). IMTN suggests that infant exposure to repeated and intense pain and stress, within the context of limited parental protection, may lead to poor neurodevelopmental outcomes. Active clinician protection to modify and minimize infant exposure to pain and stress experiences and parental-infant separation will enhance neuroprotection.

Life-saving care after birth inherently includes medical interventions and procedures to provide systemic monitoring and treatment. A side effect of many interventions and procedures, however, is pain and/or stress.

As we observed in the case of Katie Walsh, during the first 4 weeks of her life she experienced 1,633 stressful and painful events. When infants are extremely preterm and ill, parents are often unable to hold them. During this period of prolonged separation, infants experience repeated and intense pain and stress without the protective physical comfort only a parent can provide. Research has yet to identify how this lack of protective care influences brain development. Based on the scientific evidence we do have though, clinicians should seek opportunities to place infants in skin-to-skin

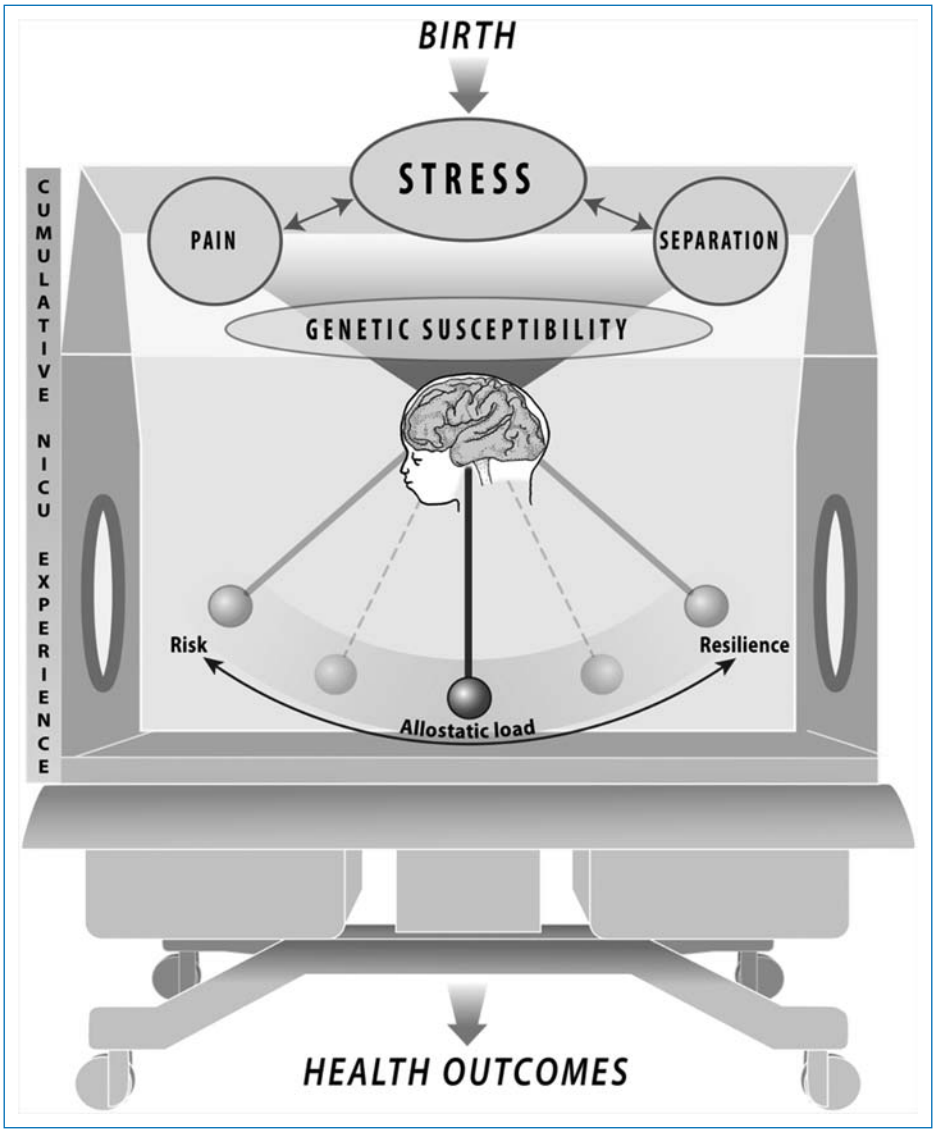

FIGURE 34.1 Infant medical trauma in the neonatal intensive care unit.

Source: D'Agata, A. L., Young, E. E., Cong, X., Grasso, D. J., & McGrath, J. M. (2016). Infant medical trauma in the neonatal intensive care unit (IMTN): A proposed concept for science and practice. *Advances in Neonatal Care, 16*(4), 289–297. doi:10.1097/ANC.0000000000000309

contact with parents as a stress reduction intervention. The potential for NICU trauma exists not only for infants but also for parents and clinicians.

Parents

Preterm birth has been described as a "traumatic event that shattered parents' taken-for-granted expectations of parenthood" (Lasiuk et al., 2013). Interestingly, the authors reported that these parents believe "stress" does not adequately describe their experience, while the term *trauma* does (Lasiuk et al., 2013). Mothers of NICU infants have been reported to experience acute stress disorder and posttraumatic stress disorder (PTSD) more frequently than mothers of full-term infants. Acute stress disorder was identified in 18% of mothers during their NICU stay, and at one month follow-up 30% of these mothers experienced PTSD (Shaw et al., 2009). At 14 months postpartum, mothers of preterm infants experienced higher rates of depression, anxiety, and traumatic symptoms (Kersting et al., 2004). Similarly, Cheng, Kotelchuck, Gerstein, Taveras, and Poehlmann-Tynan (2016) reported a higher incidence of postpartum depression in fathers of preterm infants than fathers of term infants.

From the parent perspective, preterm birth has been described as having "invisible effects" that are very difficult and involve expected milestones, connection of preterm birth to later-life consequences, relationship issues, and feelings of isolation (Graham's Foundation, 2017). The developmental milestones expected of healthy, full-term infants are often unattainable at the same age by former sick or preterm infants. For this reason, parents learn to support their child along a different chronologic continuum. As children age, it can become more difficult to distinguish a former sick or preterm infant from a healthy infant, which may or may not be beneficial. Anxiety disorders and sensory issues may also be invisible; difficulties with weight and/or growth and behavioral issues may be interpreted as bad parenting. When leg braces, a feeding tube, or thick glasses are not present, others may have difficulty recognizing correlates to preterm birth. As such, while a child's delays in meeting milestones or academic achievement may be rooted in early birth, it may not be obvious at a glance. These examples and others may ultimately lead to misunderstandings and be damaging to relationships.

Clinicians

Research has shown that clinicians who are repeatedly exposed to the suffering of others can themselves be vulnerable to compassion fatigue, secondary trauma, and PTSD. Interestingly, clinicians may not recognize their own trauma symptoms, which in turn can have significant implications in their patient care practice (D'Agata et al., 2018). Specifically, the degree to which clinicians are able to extend the qualities of compassion and empathy to others when they themselves are suffering is strained. Because patients and families rely so deeply on clinicians for compassionate, empathetic, and supportive care, when it is not received, the expectations of all parties are not met. The most important consequences of unmet expectations are the effects it can have on infants.

The demands placed on NICU clinicians to provide life-saving care can result in difficulties processing or dealing with clinical experiences of loss. Both primary and secondary traumatic stresses are recognized as adverse outcomes of providing intensive care services in healthcare providers, discussed more in depth later. A survey of NICU and pediatric intensive care providers suggested that up to 17% of participants had diagnosable PTSD and 66% had concerns that were worrisome but did not reach PTSD diagnostic criteria. Provider resilience was inversely related with clinician PTSD symptoms (Welch et al., 2016).

In a recent focus group study, more than 80% of clinicians reported having experienced a traumatic event (D'Agata et al., 2018). Participants stated they learned to "detach," suggesting that one response to vicarious traumatization in the NICU may be withdrawal of emotional responsiveness. Strategies to consider for providing protective care for the neonatal clinician include debriefings, involvement of chaplain, and training in peer support programs (Dalia, Abbas, Colville, & Brierley, 2013; Keene, Hutton, Hall, & Rushton, 2010; Welch et al., 2015). Acknowledging the nature of workplace traumatic experience for neonatal clinicians may assist in developing strategies to reduce clinician traumatization and retraumatization while promoting effective caregiver–patient and family empathy.

TRAUMA STEWARDSHIP

The Merriam Webster dictionary defines *stewardship* as "the conducting, supervising, or managing of something; especially the careful and responsible management of something entrusted to one's care." Trauma stewardship, a term coined by social worker Laura van Dernoot Lipsky, is the careful and responsible management of the trauma exposure caring professionals experience in the course of their work (Lipsky, 2009). Caring professionals include social workers, first responders, firefighters, police officers, public defenders, military persons, family caretakers, doctors, nurses, teachers, and other service providers, to name a few. Bearing witness to human suffering touches us and changes us in subtle and insidious ways that alter how we engage in our caring work. "The expectation that we can be immersed in suffering and loss daily and not be touched by it is as unrealistic as expecting to be able to walk through water without getting wet" (Remen, 1996).

The terms *burnout*, *secondary trauma*, *vicarious trauma*, and *compassion fatigue* have been used to describe the impact of trauma exposure on the professional. Burnout is usually the result of prolonged stress or frustration resulting in physical and emotional exhaustion and is usually associated with the workplace. Burnout is usually the result of prolonged stress or frustration resulting in physical and emotional exhaustion and is usually associated with unsupportive management and a compromised professional practice environment; burnout is not the result of trauma exposure. Secondary trauma occurs when the traumatizing event experienced by the patient becomes a traumatizing event for the professional with trauma exposure symptoms presenting suddenly and with little warning (Centre, 2012). Vicarious trauma and compassion fatigue are terms that have been used interchangeably to describe the impact of a specific experience and outcome (i.e., the NICU). Vicarious trauma is a permanent and pervasive change in the professional as a result of his or her empathic engagement with a patient's traumatic experience and impacts all facets of the professional's life including body, mind, character, and belief systems (Centre, 2012). For more information, see Laura Lipsky's TEDx talk entitled "Beyond the Cliff."

TABLE 34.1

TRAUMA EXPOSURE RESPONSES

Minimizing reality	Chronic fatigue and/or physical ailments
Feelings of helplessness and hopelessness	A sense that one cannot do enough
Hypervigilance	Decreased creativity
An inability to grasp complexity	An inability to listen and/or deliberate avoidance
Disconnected/dissociative moments	A sense of persecution
Feelings of guilt	Feelings of fear/fearfulness
Anger and cynicism	An inability to empathize/feeling numb
Addictions	A grandiose perception of self/an inflated sense of self-importance related to one's work

In her book *Trauma Stewardship*, Laura van Dernoot Lipsky describes 16 trauma exposure responses associated with bearing witness to and walking with victims of trauma (see Table 34.1; Lipsky, 2009). As you review the descriptions of each trauma exposure response, take note of how each description makes you feel. Embrace the opportunity this chapter provides you to cultivate trauma stewardship and take steps to restore and rejuvenate the caring-healer within. ". . . how one is with oneself affects how one is with others and, in turn, . . . how one is with others affects how one is with oneself . . ." (Watson, 2018).

Minimizing

Minimizing is about losing our compassion and our capacity to empathize with others. It is when we compare suffering or organize it into some kind of hierarchy. An example of minimizing is when we judge the degree of distress expressed by a mother based on her baby's diagnosis: "he/she just has a little TTN, what's that mother crying for, it's not like he's/she's a 24 weeker." Minimizing occurs when we are so saturated with trauma exposure we minimize trauma in order to protect ourselves from reaching our breaking point. Often, this behavior contributes to a negative organizational culture. Comparing leads to competition where we exaggerate the intensity of a given situation to make our issue more legitimate. Minimizing does not only occur at work; it can spill over into our personal lives as well, when your child comes

crying to you because she or he fell down and the response is "Stop being so dramatic, it's not like you're dying." Trauma exposure responses permeate every aspect of our lives. Minimizing the lived experience of others distances us from our shared humanity and undermines our capacity to heal. Have you noticed you or your colleagues minimizing the experience of others?

Chronic Exhaustion/Physical Ailments

The tiredness that emerges from trauma exposure induces a level of fatigue that permeates every cell of your being, a bone-tired, soul-tired, heart-tired kind of exhaustion that cannot be relieved by a good night's sleep, or a series of good night sleeps (Lipsky, 2009). This severity of exhaustion is observed in people who feel completely overwhelmed by the urgency of their work and the belief they have no choice about the work they do. "The fresh-scrubbed and hopeful idealism of the new [nurse] starting out may gradually give way to a thrashed, haggard, martyred persona" (Lipsky, 2009).

In *The Body Keeps the Score*, Bessel Van Der Kolk (2014), the author, reveals the internal toll trauma has on how we think, feel, and respond to everyday situations as a result of our trauma exposure (Van Der Kolk, 2014). Trauma produces actual physiologic changes, including a recalibration of our hypothalamic-pituitary-adrenal (HPA) axis (our internal alarm system), an increase in stress hormones, and alterations in the systems that filter relevant information from irrelevant information. These physiologic changes impact our health and wellness and manifest in not only chronic fatigue, but also chronic pain and body aches, migraines, hypertension, obesity, and other chronic morbidities. What types of restorative self-care practices do you or could you employ on a regular basis to shield yourself from chronic exhaustion?

Feelings of Helplessness and Hopelessness

Feelings of helplessness and hopelessness are experienced when the positive aspects of work are eclipsed by the negative (Lipsky, 2009). It may be that feeling of successfully resuscitating an infant at the cusp of viability but knowing that the next few days will likely be filled with uncertainty. Garber and Seligman (1980) identified three perceptions that contribute to feelings of helplessness: (1) the perception of being personally responsible for a bad outcome even when this is unreasonable; (2) the perception that there is no relief from the current reality of the traumatic event/crisis; and (3) the perception that you are likely to repeat your current struggle in another time and place; there is no escape. Do any of these perceptions resonate with you?

A Sense That One Can Never Do Enough

"If I don't do it, it's not going to get done, and if it doesn't get done, babies will die. I can never do enough." How many times have you made or heard that statement? The belief that no matter what you do, it will not be enough wreaks havoc in our lives and instills a powerful sense of inadequacy. This sense of inadequacy plays itself out in organizational cultures that perpetuate a culture of scarcity: "We don't have enough staff, we don't have enough money, you need to work harder, you need to work more, and it still won't be enough." These negative, oppressive messages undermine our ability to recognize our self-worth and feel validated about the good work we do, leaving us dissatisfied in our work and maybe in our life. What would it look like for you to be satisfied in your work, in your life? How can you create that?

Hypervigilance

Hypervigilance creates a dynamic where we are so focused on the work we are unable to be present for anything else in our life; it is an attempt to restore a sense of safety and control by anticipating everything as a possible threat, waiting for the other shoe to fall, so to speak. In the NICU, the ever-present potential for life threat can cultivate hypervigilance. Individual experiences with different clinical scenarios may create a state of hyperarousal, which can include hypervigilance and heightened anxiety. Remember, the first thing to do in a code is to take your own pulse. Taking your own pulse brings you back to center, brings you to the present. Being present allows you to regulate your autonomic nervous system, which then enables you to act instead of react. Joan Halifax, an American Zen Buddhist teacher, worked with palliative care and end-of-life nurses and introduced G.R.A.C.E. as an intervention to reduce compassion fatigue among this unique group of health professionals. The "G" stands for *gather your attention*; the "R" invites you to *recall your intention*; the "A" is *attune* to the individual or situation; "C" means to *consider* what you should do, based on your attunement; and the "E" is to *engage and then end* the encounter (Halifax, 2014). Practicing G.R.A.C.E. takes just a few minutes but creates the opportunity for you to center yourself and be present. Try G.R.A.C.E. during your next shift and see if anything changes within you.

Diminished Creativity

"The deeper we sink into a culture of trauma, the less flexible and original our thinking becomes." (Lipsky, 2009). Change requires creativity, and with creativity comes a certain amount of chaos or uncertainty that may feel threatening. When we experience trauma exposure, we find ourselves thirsty for structure and stability and become resistant to change, even if the change is evidence-based. Is it possible that a culture of trauma may be a contributing factor to a knowledge–practice gap as we resist change to create a false sense of control? What could you do to cultivate creativity in your unit?

Inability to Grasp Complexity

A strong indicator of the inability to grasp complexity is when we look for clear signs of good or bad, right or wrong, yes or no. It is when we are unable to grasp the entirety of a given situation that we take sides, internalizing a binary structure to help us cope with the complexities inherent in healthcare. The toll of bearing witness reduces our capacity to engage with the nuances and gray areas of the human experience of crisis. We all know the importance of the family to our fragile patients, yet what the family brings to our work can be too overwhelming to integrate into our workflow. As a result, we create rules, guidelines, and policies to restrict and define when, where, and how family is allowed to engage and parent their hospitalized infant. Life is messy, but it is the messiness that becomes cognitively impossible to grasp when we are exposed to trauma day after day (Lipsky, 2009). Practicing personal wholeness enables us to make room within ourselves to embrace the complexity of the human condition. How do you practice personal wholeness?

Inability to Listen/Deliberate Avoidance

Avoidance may be seen as quickly finishing up your hands-on care to avoid facilitating a parenting moment when the family comes in "a little too late" (according to you) to provide skin-to-skin care with their baby. It is finishing up all your tasks so you can sit in the rocking chair and wait for the next round of caregiving. The inability to listen (a form of avoiding engagement with others) can be observed when someone may be speaking to you, but the only thing going on in your head is what your next task is and you shut down the "conversation" with a swift and often curt retort.

As avoidance shows up in your personal life, you may go out less and less or if you do go out, it is with people who are as avoidant as you are, people who "get it" (Lipsky, 2009). Has avoidance crept into your daily routine?

Dissociative Moments

A dissociative moment is the experience of being engaged in your work and then, for whatever reason, suddenly something inside you becomes unhinged (Lipsky, 2009). You realize you have disconnected with what is happening right in front of you. A NICU example could be you are running a code, and all of a sudden you remember the last infant you unsuccessfully resuscitated. These moments are common and only become problematic when we try and "tough it out" by pretending not to feel. No matter what role you play in the NICU, when you are exposed to the suffering of others, you can expect these moments to occur. Notice them, avoid isolation, and seek out the support you need to stay whole and healthy. How does your unit support staff who have experienced the loss of a patient? Do you routinely debrief after critical events?

Sense of Persecution

Feelings of persecution arise from a profound lack of self-efficacy in one's life and we become convinced that we are unable to change our circumstances (Lipsky, 2009). When we succumb to the belief that we cannot change our situation, we consent to suffer and relinquish our power to an outside force (Lipsky, 2009). This is the "martyr mentality." Sometimes we can feel persecuted by our own patients and their families: "Why does this kid always need a new IV when I am on?"; "Why does this family always want to kangaroo when I have a busy assignment?" Quickly and insidiously, we can forget how tragic it must be to require neonatal intensive care, to have your baby fighting for his or her life, to be confused, frightened, and alone being cared for by strangers. Uncovering persecution as a trauma-exposure response often shows up in the language we use to describe our circumstances. What language is used in your NICU that may suggest you or your colleagues are experiencing a sense of persecution?

Guilt

Bearing witness to the suffering of the infants and families we serve in the NICU can sometimes make us feel guilty that our life is pretty good, maybe our family is healthy, we have a great support network, or simply that we can leave the hospital at the end of our shift. One of the bad things about guilt is that it undermines our ability for authentic connection with others (Lipsky, 2009). We may find ourselves not wanting to share information about our vacation or time off with our patient's family because we do not want to make them feel bad. However, purposefully diminishing ourselves will not help us make the connections that are so important in the work we do. Being honest, not pretentious, about our privilege allows us to be present and experience our shared humanity with others (Lipsky, 2009). This simple act can actually provide comfort and connection, which is what we all need, especially when we are in crisis. How do you create authentic connection with the infants and families you care for?

Fear

Fear is a natural response to much of what we witness in our work: fear of intense feelings, personal vulnerability, or potential victimization (Lipsky, 2009). In our opening scenario, I am sure the clinicians in Katie's delivery room experienced some degree of fear as she emerged blue and limp and required resuscitation. When feelings of fear (which are perfectly healthy) are not addressed, discussed, and released, they can turn into anger and prejudice (think of perinatal substance use and neonatal abstinence syndrome). These prejudices quickly morph into stereotypes and lead to generalizations about cultures and socioeconomic groups (Lipsky, 2009). These generalizations undermine our ability to serve. Fear makes us feel vulnerable, which is uncomfortable, and so quite often we distance ourselves from those feelings. However, when we are able to acknowledge our fear, it deepens our capacity for compassion, for ourselves and others. Have you experienced fear in the course of your work? How have you worked through your fear?

Anger and Cynicism

"Anger is a common feeling among those trying to do right in the world" (Lipsky, 2009, p. 101). Whether your anger is a flash of rage or a slow boil, it is important to understand what your anger looks like so that you can learn to manage it. When we are not connected to what our anger looks like, we can often direct it to people and situations unrelated to why we are angry. In the clinical setting, an example may be how we behave with certain families or diagnoses that spark our anger, but really are not the root of our anger. Cynicism, on the other hand, has been described as a sophisticated coping mechanism for dealing with anger and is often witty and easy to laugh at (Lipsky, 2009). Cynical humor is a way to avoid dealing with our feelings of anger; although alluring, it can warp our sense of the world around us. We may get angry when our patients exhibit physiologic instability while providing hands on care but then glibly comment that they "tried to die on us." That kind of cynical response reflects a complete absence of empathy fueled by a failure to address our underlying feelings of anger. Have you experienced anger in the course of your work? What does your anger look like?

Inability to Empathize/Numbing

The inability to empathize is the result of a system that is completely overwhelmed with constant input. Likened to a sponge, when we have reached the point of saturation we are unable to take in any more input and we become numb (Lipsky, 2009). We become afraid to feel, as if the feelings will come in torrents that we will not be able to control. Sometimes we become so used to not feeling that when we are removed from our day-to-day routine, for example on vacation, we may struggle to really enjoy ourselves (Lipsky, 2009). Have you experienced an inability to empathize with your patients and their families? What would help you reconnect with your feelings in a way that did not overwhelm you?

Addictions

"An addiction is an attachment so strong that it persists despite our understanding of its potentially destructive nature" (Lipsky, 2009, p. 109). Often when we think of addiction, we think of the usual suspects (alcohol, drugs, food, and sex), but many of us may also have an addiction to the rush of adrenaline we experience in our work. Overwork is an example of addiction that keeps us from feeling and being with the world around us. However, at some point, our efforts to escape the intense feelings associated with our work are unable to be held back by our addiction. What are you most attached to? How does this attachment serve you and others?

Grandiosity: An Inflated Sense of Importance Related to One's Work

"When work becomes the center of our identity, it may be because it feeds our sense of grandiosity" (Lipsky, 2009, p. 111). We must approach with caution our reliance on work for our sense of

self-esteem. This certainly may be a challenge in the United States where our work is a cornerstone of our self-image, especially when we do such important work as seen in the NICU. Losing ourselves to our work means we have truly lost our self. We are more than nurses; we may be mothers, fathers, friends, brothers, sisters, joggers, swimmers, artists; we may be many of these things and often more. Maintaining a sense of balance between all the facets of who we are enables us to preserve our wholeness and our integrity. What you do is not who you are (Lipsky, 2009). How do you stay grounded in the larger reality of your life?

Recap

The onset of trauma exposure responses is often insidious and even invisible in settings that lack awareness about the physiologic and psychologic sequelae of bearing witness to suffering on a regular basis. Mediated by the HPA axis, chronic exposure to toxic stress has a cumulative negative effect on health and wellness across the life span. Trauma stewardship and the concept of trauma-informed care in the NICU have implications for mitigating these deleterious effects on the infant, the family, and ourselves. While bearing witness is a moral way of engaging with our patients and their families (Naef, 2006), we must be cognizant of the toll it takes on us and adopt self-care practices that help us find balance, create a sense of personal control, make healthy lifestyle choices, and ensure a supportive social network (Lipsky, 2009).

WHY IS IT IMPORTANT TO REDUCE THE TOXIC STRESS ASSOCIATED WITH TRAUMA?

Stress is a word many of us commonly use to describe physically and emotionally taxing experiences (McEwen, 2007). In our culture today, we often use the word *stress* as a descriptor of all different types of events in our daily lives. This common and varied usage of the word has the potential to perhaps desensitize us to important effects of this brain–body reaction to stimuli.

Stress can be differentiated into "good or positive" and "bad or negative" stress, indicating the benefit or burden of the experience. As we discuss later, the duration of stress exposure is another important differentiator between acute and chronic stress. Despite the quality of the stress experience, the same physiologic activation occurs in our bodies—activation that includes reactivity of the autonomic nervous system and HPA axis. The physiologic response to stress exposure is a highly complex process that is not covered in detail here. In turn, we refer interested readers to literature by Dr. Bruce McEwen (McEwen, 2004, 2007).

In response to stress, hormones, inflammatory mediators, and neurotransmitters are released to support our *fight or flight* response and eventual decay of the chemical response. There are critical factors of the stress response that include inadequate or excessive responsivity, as well as the frequency of response activation. If one's physiologic response to stress is blunted, there is an inability to mount an appropriate response. Conversely, for some people, stress exposure produces a physiologic response that is in excess of what would normally be expected. The reason for inappropriate responses may be due to the frequency of activation. When we encounter chronic stress, it may affect how we respond to future stress. The stress event initiates a hormone, neurotransmitter, and autonomic response. As the event resolves, the chemical response decreases and the body begins to return to baseline. When one encounters repeated events or "hits," the stress response system is in constant activation, allowing for little recovery. Figure 34.2 demonstrates normal and abnormal stress responses.

This background information on how our bodies respond to stress is important when we consider NICU infants and trauma. The literature reports a range of daily stressful and painful events for infants cared for in the NICU. Carbajal et al. (2008) reported that in an Italian cohort of 430 NICU infants with a mean gestational age of 33 weeks, infants experienced an average of 141 procedures during their NICU stay, 78 of which were painful. Additionally, these infants experienced an average of 16 procedures per day, 12 of which were painful. In a small cohort, D'Agata et al. (2017) combined stressful and painful procedures and reported NICU infants, with a mean gestational age of 30 weeks, experienced an average of 46 events per day. Variability among reports of NICU infant painful and stressful events is often related to clinical practice of units, the country where the study was conducted, and the types and quantity of procedures included in the data collection. Regardless, these reports demonstrate chronic stress experiences that occur to infants simultaneously during key critical and sensitive periods of brain development and maturation, placing infants in very vulnerable situations (Exhibit 34.4).

For preterm infants who experience repeated NICU stress exposure, functional and structural changes to their brain may occur. Smith et al. (2011) examined NICU infant stress exposure and found frontal and parietal regions of the brain to be decreased in size (Smith et al., 2011). Furthermore, alterations in the microstructure were noted. When neurobehavior was evaluated at term age, infants demonstrated at-risk behaviors, consistent with early life stress exposure (Smith et al., 2011). Using MRI at term-equivalent, Chau et al. (2013) found abnormal brain development with infants born at 24 to 32 weeks' gestation. When these infants were 18 months old, abnormal brain development was associated with adverse neurodevelopmental outcomes (Chau et al., 2013). The complex relationship of early life medical care and stress exposure reflect an environmental burden that may influence health and neurodevelopmental outcomes.

Sullivan and her colleagues have followed a cohort of preterm infants from birth to 23 years of age. During their early school age years, as expected, preterm survivors with neurologic compromise demonstrated increased impairment and poorer cognitive performance (McGrath, Sullivan, Lester, & Oh, 2000). At 12 years of age, neonatal morbidities continued to impact the health of survivors (Miller, Sullivan, Hawes, & Marks, 2009). As adolescents, high rates of depression, anxiety, and attention problems were identified (Sullivan, Msall, & Miller, 2012). At 23 years of age, young adults who were born preterm and experienced neonatal illness demonstrated distinctly different cortisol patterns from term-born peers (Winchester, Sullivan, Roberts, & Granger, 2016). Interestingly, preterm infants considered "healthy" demonstrated a most unique cortisol pattern. The health trajectory of this former preterm cohort supports the theory that early life stress disrupts the developing brain and HPA axis, resulting in later life dysregulation. Dysfunction and dysregulation during the neonatal period place these individuals at increased risk for issues later in life with cognition, mental health, and other stress-related diseases.

In 1998, Felitti et al. published a landmark study describing the long-term health effects of adverse childhood exposures. Adverse childhood experiences (ACE) are events of abuse and environmental exposures that have associations to adult mental health and disease risks (see Box 34.2). Using adult self-reports of childhood abuse, researchers asked participants about occurrences of neglect, parent mental illness, parent substance abuse, and witness to domestic violence and found a strong dose response with multiple adult health risks. These health risks included heart disease, cancer, and chronic lung disease. Interestingly, of the greater than 50% of adults who reported a history of childhood exposure, they also reported

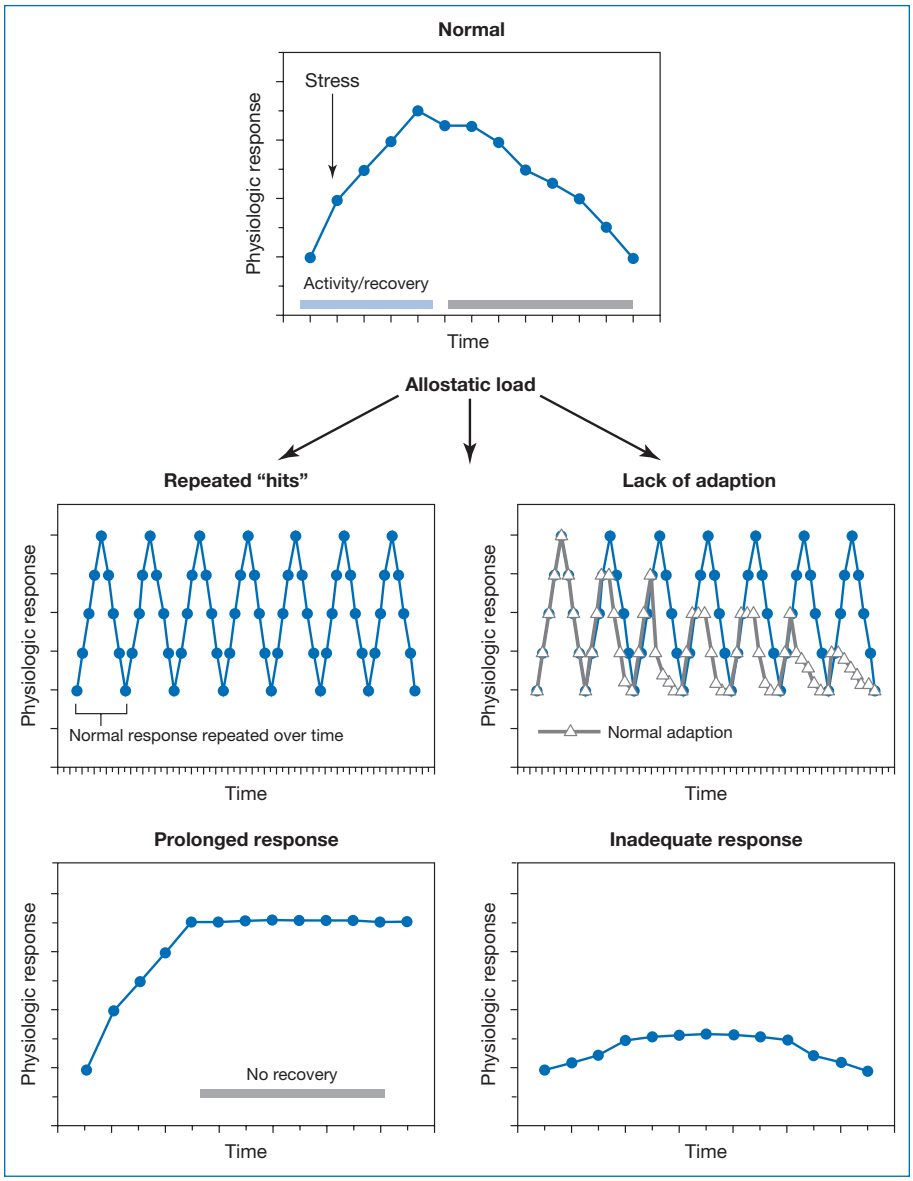

FIGURE 34.2 Four types of allostatic load.

Source: With permission from McEwen, B. S. (2007). Physiology and neurobiology of stress and adaptation: Central role of the brain. *Physiological Reviews, 87*(3), 873–904. doi:10.1152/physrev.00041.2006

EXHIBIT 34.4

COMMON INTERVENTIONS AND PROCEDURES FOR PRETERM INFANTS

You may be asking yourself what about the NICU experience is so stressful that it would cause brain changes. Let us think about Baby Walsh in our opening scenario. A baby born at 23 weeks will most likely receive this type of immediate life-saving care following delivery:

- Transfer to a far different environment than the uterus.
- Bright lights, loud voices and commotion, cool temperatures, touching, and repeated movement of a fragile body
- Intubation at birth, success on third attempt
- Repeated oral and nasal suctioning
- Umbilical line placement
- Transport through hallways and elevators to NICU with often unsteady control of endotracheal tube
- Positioning and repositioning for x-rays
- Frequent interruption of rest for assessments
- Heelsticks for glucose testing

These interventions and procedures are commonplace to NICU clinicians and reflect lifesaving procedural practices we have been trained to perform. In addition, we typically complete these initial procedures as quickly as are tolerable to the infant. A momentary pause to consider how stressful and painful this series of clinical interventions likely is to a fragile 23-week infant is a simple first step to practicing trauma-informed care.

more than one type of abuse. This demonstrates that as exposures increased, the risk for obesity, depression, and suicide attempt also increased. The more exposures a child has to adverse events, the greater the possibility of developing adult physical and mental health sequelae.

While the Felitti et al. study was not conducted with former preterm infants, this type of research demonstrates the risks posed to one's health when children are exposed to adverse events at a critical stage of development. As previously discussed, preterm infants are exposed to prolonged and intense pain and stress events during NICU care. They have few coping mechanisms, minimal maternal contact, and no agency; all of this coupled with their immature brain development suggests that these infants are at significant risk for toxic stress. The major concern from toxic stress exposure for preterm infants is the developmental implication. Former very preterm infants subject to greater invasive and painful procedures evaluated at age 7 demonstrated decreased cerebellar volume and poorer cognition (Ranger et al., 2015).

Molecular evidence is also beginning to emerge that suggests various preterm infant systems may be impacted by early life experience. In particular, DNA methylation changes (Giarraputo et al., 2017; Montirosso, Provenzi, et al., 2016), dysbiosis of the gut microbiome (Chernikova et al., 2018; D'Agata, Wu, et al., 2019; Dahl et al., 2018), and cortisol reactivity (D'Agata, Roberts, et al., 2019; Grunau, 2013; Vittner et al., 2017), to name a few, generally confer early life exposures leading to short-term alterations. What has yet to be determined are the mechanisms by which these changes may influence longer-term outcomes (Figure 34.3; Johnson, Riley, Granger, & Riis, 2013).

These findings are compelling not only to health professionals but also to parents. As evidence continues to be elucidated as to the impact of early life experience of preterm infants, and how environmental exposures influence neurobiology, the NICU will be confronted with how to improve practice to better support infants. If clinicians do not demand re-evaluation of practice norms and

Box 34.2

EXAMPLES OF ADVERSE CHILDHOOD EXPERIENCES

- Physical abuse
- Sexual abuse
- Emotional abuse
- Physical neglect
- Emotional neglect
- Intimate partner violence
- Mother treated violently
- Substance misuse within household
- Household mental illness
- Parental separation or divorce
- Incarcerated household member

Source: Retrieved from https://www.cdc.gov/violenceprevention/childabuseandneglect/acestudy/aboutace.html

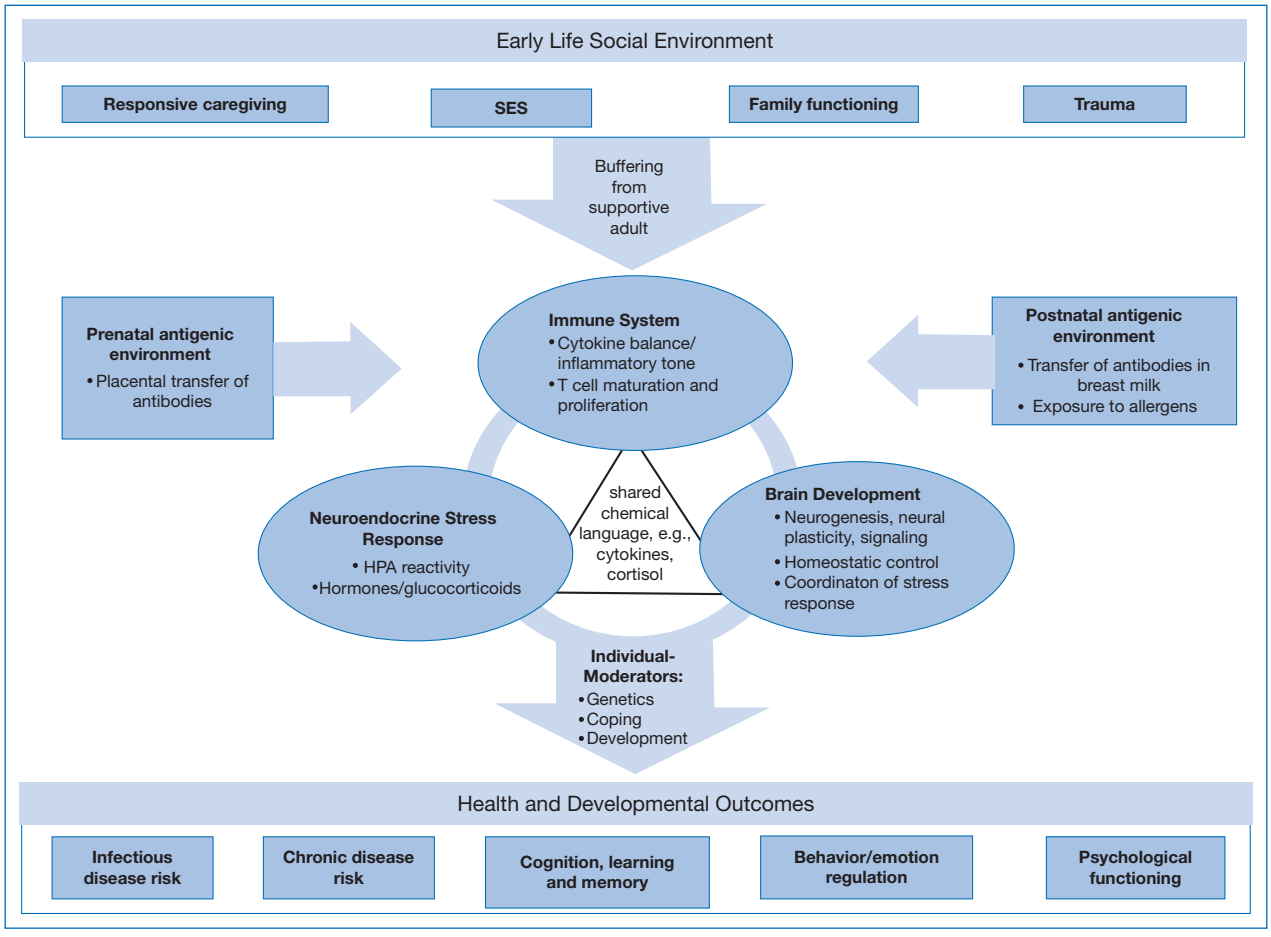

FIGURE 34.3 Model of neuroendocrine immune network as mediator linking early life experiences to health and developmental outcomes.

HPA, hypothalamic-pituitary-adrenal; SES, socioeconomic status.

Source: Johnson, S. B., Riley, A. W., Granger, D. A., & Riis, J. (2013). The science of early life toxic stress for pediatric practice and advocacy. *Pediatrics, 131*(2), 319–327. doi:10.1542/peds.2012-0469

standards of care, parents will likely demand it of us. Thus, the implications for advancing practice affects not only nursing but also all those who care for vulnerable preterm infants. To help meet the expectations of the patients and families we serve, we must begin to look at the NICU through their lens and consider how we might modify practice to be more neuroprotective.

TRAUMA-INFORMED NEUROPROTECTIVE CARE

Trauma-informed neuroprotective care (TINC): (a) ***realizes*** that traumatic experiences change our biology; (b) ***recognizes*** the signs and symptoms of trauma in patients, families, colleagues, and others involved in caregiving; (c) ***responds*** by fully integrating knowledge about trauma into policies, procedures, and practices; (d) actively seeks to ***resist retraumatization*** (SAMHSA, 2014). Retraumatization is a conscious or unconscious reminder of past trauma resulting in a re-experiencing of the initial trauma event that can be triggered by an action, attitude, or expression that makes one feel powerless and compromises a felt sense of safety (Exhibit 34.5).

Realization that Trauma Changes our Biology

Our opening story about Katie Walsh exemplifies the how the trauma experienced in the NICU changed Katie's biology: "*Early on, Katie was diagnosed with learning and sensory processing challenges, attention deficit disorder, and executive function disorder. Most recently, Katie has shared with the nurses her struggles with anxiety and depression and was diagnosed with major depressive disorder last year.*"

Recognizing Signs and Symptoms of Trauma

Signs and symptoms of toxic stress and trauma experienced by NICU infants and families are shown in Table 34.2. For signs and symptoms of toxic stress and trauma experienced by the clinician, see Table 34.1.

While the list in Table 34.2 is far from exhaustive, it highlights signs and symptoms of infant and parent traumatic stress that are often misinterpreted in the setting of the NICU. Our own trauma exposure increases our vulnerability to minimizing the lived experience of the families we serve as we become numb and less capable of empathizing with others.

Response to Trauma

The response to trauma in the NICU (under a TINC paradigm) is the adoption and integration of evidence-based best practices in TINC aimed at managing, mitigating, and minimizing the trauma experience of the infant, the family, and the clinician (Coughlin, 2016). These best practices must be reflected in policies, procedures, practice guidelines, documentation requirements, and ongoing staff education and new hire orientation curriculum.

Resisting Retraumatization

Infants and neonates are capable of experiencing intense pain and show signs of traumatization (Coates, 2016). The memories of these events are stored in such a way that affect learning and behavior later in life, consequently adopting a trauma-informed approach to care in the NICU is paramount (Coates, 2016).

Of critical importance, once a trauma-informed care paradigm is established, there must be a commitment to sustain this new culture of care over time. Sustaining the gains in transforming the culture of care is achieved through clear accountability metrics, ongoing practice audits, and integrating the principles and values of TINC into daily practices across all disciplines that interface with the NICU patient and family population.

Quality Core Measures for Trauma-Informed Neuroprotective Care

Inconsistent definition, application, and evaluation of developmentally supportive care prompted the development of core measures for developmentally supportive care in the NICU (Coughlin, Gibbins, & Hoath, 2009). Coughlin et al. (2009) adopted The Joint

EXHIBIT 34.5

Retraumatization in the NICU

Jake Walsh brought Katie back to the NICU when she had just turned 1 to visit Tracy, Shannon, and Erin. The minute the elevator doors opened on the second floor, where the NICU was located, Katie's demeanor changed and she began fidgeting and fussing. The closer they got to the NICU reception area, the more agitated and distressed Katie became.

TABLE 34.2

SIGNS AND SYMPTOMS OF TOXIC STRESS AND TRAUMA

Infants	Families
Exaggerated responses to acute stress; intense fight or flight responses (Holsti, Grunau, Whitfiled, Oberlander, & Lindh, 2006; Vinall & Grunau, 2014; Whitfield & Grunau, 2000)	Feelings of guilt and inadequacy in parental role (Lasiuk, 2013; Roque, Lasiuk, Radunz, & Hegadoren, 2017)
Hyporeactivity and/or immobilization to increasing stress; fright and freeze responses (Whitfield & Grunau, 2000)	Less affectionate and less responsive to their infant; withdrawn, flat affect, and/or hostility or intrusiveness with their infant (Tahirkheli, Cherry, Tackett, McCaffree, & Gillaspy, 2014)
Feeding intolerance (Moore & Pickler, 2017; Moore et al., 2013)	Fatigue and sleep disruptions (Busse, Stromgren, Thorngate, & Thomas, 2013)
Sympathetic nervous system arousal (Holsti, Gruanu, Oberlander, & Whitfield, 2005)	Protracted sadness and worry (Greene et al., 2015)
Autonomic dysregulation (Grunau et al., 2005)	Hypervigilance and avoidance behaviors (Greene et al., 2015)
Poor weight gain (Godoy, Rossignoli, Delfino-Pereira, Garcia-Cairasco, & de Lima Umeoka, 2018)	Physical and emotional withdrawal (Flacking et al., 2012)

Commission framework of core measures to establish disease-independent, minimum, evidence-based best practice standards that would offer an objective basis for cross-institutional comparison of developmentally supportive care practices. In 2011, these core measures became the National Association of Neonatal Nurses' (NANN) *Age-Appropriate Care of the Premature and Critically Ill Hospitalized Infant: Guideline for Practice* (Coughlin, 2011) and have been recognized internationally as best practice standards for developmentally supportive neuroprotective care in the NICU (Milette, Martel, da Silva, & Coughlin McNeil, 2017a, 2017b). The concept of trauma-informed care for hospitalized infants resonates with neonatal clinicians and researchers around the globe (Coughlin, 2014; Montirosso et al., 2012; Torowicz, Lisanti, Rim, & Medoff-Cooper, 2012). In 2016, NANN endorsed *Trauma-Informed Care in the NICU: Evidence-Based Practice Guidelines for Neonatal Clinicians* (Coughlin, 2016).

There are five core measure sets for trauma-informed care. These categories of quality caring have remained consistent since their inception in 2009; however, the attributes and specific criteria for each core measure set have evolved as more and more evidence has been brought to bear on what constitutes best practice in (a) the healing environment; (b) protected sleep; (c) pain and stress prevention, assessment and management, and the role of the family; (d) activities of daily living: posture and mobility, eating experiences, skin care, and hygiene; and (e) family collaborative care (see Figure 34.4 and Table 34.3).

In a large, multicenter, longitudinal study on the quality of developmentally supportive, neuroprotective care, Montirosso, Tronick, and Borgatti (2016) demonstrated both short- and long-term implications of high-quality developmentally supportive neuroprotective care (see Table 34.4). These findings highlight the importance of quality and consistency in improving outcomes.

Nursing in the NICU

While it is clear that a cultural shift must occur to achieve the best results from a trauma-informed care paradigm, a change of attitude and mindset that supports and ensures a holistic, person-centered approach to caring must be embraced by all who work in the NICU. For nursing, this shift restores the primacy of nursing care—to support and manage the human experience of disease. Watson (2018) urges nursing to move beyond "practice-for-institutional-practice's sake to praxis – an informed moral practice guided by our timeless values . . . and love of humanity . . . and all its complexities and unknowns." If we fail to do this, we

FIGURE 34.4 The five core measure sets for trauma-informed care.

Source: Caring Essentials Collaborative. (2018). *Trauma-informed, neuroprotective care for hospitalized infants, families, and staff.* Retrieved from https://www.caringessentials.net

TABLE 34.3

QUALITY CORE MEASURE SETS AND ATTRIBUTES FOR TRAUMA-INFORMED NEUROPROTECTIVE CARE IN THE NICU

Healing environment	• The physical environment is conducive to rest, healing, and establishing relationships that confer a sense of safety and connectedness. • The healthcare team is collaborative, respectful, mindful, and caring. • The Organizational Environment reflects a just culture committed to quality and safety.
Pain and stress	• Prevention of pain and stress is a daily expressed goal. • Continuous and procedural pain and stress are routinely assessed, managed, and reassessed to ensure maximum infant comfort. • Family is informed and involved in managing and mitigating the pain and stress of their infant(s).
Protected sleep	• Infant sleep and diurnal rhythmicity are protected and supported. • Sleep protective strategies are implemented in partnership with parents and family. • Staff role-model compliance with safe sleep practices for eligible infants.
Activities of daily living	• Postural alignment and spontaneous movement are supported for optimal comfort, safety, and neuromotor development. • Infant eating experiences are nurturing, individualized, infant-driven, and pain and stress free. • Skin care routines preserve barrier function and ensure tissue integrity.
Family collaborative care	• Parents and family, integral to quality care, have unrestricted access to their infant(s). • Emotional well-being of parents and families is routinely assessed and supported with access to appropriate, culturally sensitive resources. • Parenting skills are mentored, supported, and validated throughout the hospital experience.

may lose our identity as caring healers and become very good technicians subsumed by other disciplines (Watson, 2018).

The seductive lure of a technologically advanced environment juxtaposed with the ever-present threat of death and dying can make us lose sight of our purpose and our passion—to be the difference in the life of another. Several of the trauma-exposure responses (Table 34.1) gain traction when we lose ourselves in a complex web of the suffering savior. In order to be the best version of ourselves and fully operationalize our purpose and passion, we must be present in every human encounter. Embracing the quality core measures for TINC creates opportunities for us to be present and to transform the experience of care for each baby and family we serve.

> *"The nurse is responsible for creating and maintaining an environment conducive to the healing process."—Nightingale, 1860*, p. 8

TABLE 34.4

TIME OF ASSESSMENT, OUTCOME MEASURE, AND MAIN FINDINGS OF NEONATAL ADEQUATE CARE FOR QUALITY OF LIFE STUDY UP TO 60 MONTHS AGE OF PRETERM CHILDREN

		Quality of Neuroprotective Care	
Time of Assessment	**Outcome Measure**	**High Infant-Centered Care Practices**	**High Infant Pain Management Practices**
At NICU discharge	Neurobehavioral profile	Higher regulation Lower excitability Lower stress/abstinence	More attention and arousal Lower lethargy Fewer nonoptimal reflexes
Eighteen months corrected age	Behavioral problems	No effect	Lower internalizing problems
Thirty-six months corrected age	Language skills	Comprehension of sentence	No effect
Sixty months corrected age	Health-related quality of life	Higher health-related quality of life score on social, motor, and emotional functioning	No effect

Source: Modified from Montirosso, R., Tronick, E., & Borgatti, R. (2016). Promoting neuroprotective care in neonatal intensive care units and preterm infant development: Insights from the neonatal adequate care for quality of life study. *Child Development Perspectives, 11*(1), 9–15. doi:10.1111/cdep.12208

TABLE 34.5

THE CLINICIAN'S TOOLBOX FOR TRAUMA-INFORMED CARE PROVIDES THE READER WITH QUALITY CORE MEASURES, ATTRIBUTES, AND SUGGESTED NURSING ACTIONS

The Healing Environment		
Attribute	**Criteria**	**Nursing Actions**
Physical environment	• Sensory input (e.g. light, sound, touch etc.) is age-appropriate; dose and duration of sensory input is guided by the infant's behavioral and physiologic responses. • Space safely accommodates the provision of quality clinical care, 24-hour parental presence, and privacy. • The design of the space honors the holistic and human dimensions of those that inhabit it, integrates stress-reducing strategies, and facilitates social and therapeutic interactions for patients, families, and professionals.	• Use a speaking voice in the infant care area that aligns with AAP sound level recommendations (e.g., use your library voice or your church voice) • Invite parents to decorate their baby's bedspace • Explore the availability of stress-reducing resources for families and staff—music therapists, quiet rooms for meditation, outdoor gardens, etc.
Human environment	• The interprofessional team exhibits shared responsibility in problem solving and decision making to formulate holistic plans for patient care; team members assume complementary roles that facilitate cooperation. • Team members support each other in "always doing the right thing" for the patient, the family, and staff. • All verbal, written, and behavioral communication is respectful, complete, and patient-centered; there is zero tolerance for behaviors that compromise safety and/or undermine respectful relationships.	• Practice mindful presence • Ask for help—for the sake of the patient • Provide help, even when not asked • Consider incorporating G.R.A.C.E. into your caregiving routine

(*continued*)

TABLE 34.5

THE CLINICIAN'S TOOLBOX FOR TRAUMA-INFORMED CARE PROVIDES THE READER WITH QUALITY CORE MEASURES, ATTRIBUTES, AND SUGGESTED NURSING ACTIONS (*continued*)

The Healing Environment		
Attribute	**Criteria**	**Nursing Actions**
Organizational environment	• Core measures for age-appropriate care provide the standard of care for all patient care encounters and are reviewed/revised annually to reflect the latest evidence-based best practices. • Practice standards are integrated into the annual performance evaluation across all disciplines and professionals who interface with the neonatal/infant population. • A just culture framework ensures balanced accountability at the individual and organizational levels for continuous learning, quality improvement, and patient safety.	• Join your unit/hospital practice council • Take ownership for the professional practice in your setting • Be a mentor to your colleagues, both new and legacy
Protected Sleep		
Protect sleep integrity	• Scheduled, nonemergent caregiving is contingent on the infant's sleep–wake state and adapted accordingly. • Cycled lighting is provided to support circadian rhythms. • Staff and family are competent in the assessment of infant sleep–wake states.	• Change your mindset from technician to healer and use the scheduled caregiving times as a lattice to your caring encounters instead of a prescription • Educate yourself about sleep and wake behaviors and use this new knowledge to guide your caring encounters
Support sleep	• Skin-to-skin care is an integral part of the daily care of eligible infants; length of sessions are documented in the medical record. • An individualized sleep hygiene routine is an integral part of daily care. • Supportive sleep routines are developed in partnership with family and documented to ensure consistency.	• Gain confidence and competence in facilitating skin-to-skin experiences • Offer skin-to-skin care *always* for eligible infants • Support parent confidence in providing skin-to-skin care • Collaborate with parents to create daily routines that facilitate transition to home
Safe sleep	• All staff are competent in the most current "back to sleep" recommendations from the AAP; competency is documented. • There is a clear protocol and/or algorithm for the transition and initiation of "back to sleep" practices. • Parents demonstrate competency in safe sleep practices before their infant is discharged home.	• Role model safe sleep practices for parents and colleagues • Ask questions when safe sleep practice is not adopted for eligible infants • Support parent confidence in safe sleep practices
Pain and Stress		
Prevention	• Painful and/or stressful daily activities are critically reviewed, revised, and modified based on the infant's current health status. • Each infant will have an individualized pain and stress prevention care plan that will be reviewed daily with the interprofessional team. • A unit-specific pain and stress prevention policy will address strategies to manage disease-specific pain (abdominal, pulmonary, neurologic, etc.) as well as pain and/or distress associated with hunger, gas, pruritus, and other discomforts experienced during hospitalization and critical illness.	• Ask if the painful procedures that are scheduled for any given day are actually necessary; if so, coordinate with parents to provide comfort during the procedure(s) • Draft a pain and stress prevention policy for your unit, engage your colleagues to join the initiative; gain buy-in from key stakeholders—test, refine, implement, and measure
Assessment and management	• A valid, age-appropriate, contextually accurate pain assessment tool is used for all patient care encounters throughout the hospital stay. • Pain and stress assessments guide all caregiving activities; caregiving activities are adapted and modified based on infant physiologic and biobehavioral expressions.	• Know your unit's pain assessment tool; truly assess the infant during its experience of pain/distress and respond accordingly

(*continued*)

TABLE 34.5

THE CLINICIAN'S TOOLBOX FOR TRAUMA-INFORMED CARE PROVIDES THE READER WITH QUALITY CORE MEASURES, ATTRIBUTES, AND SUGGESTED NURSING ACTIONS (*continued*)

Pain and Stress		
Attribute	**Criteria**	**Nursing Actions**
Assessment and management (*cont.*)	• Nonpharmacologic and/or pharmacologic pain and/or stress-relieving strategies are consistently and reliably provided for *all* painful and/or stressful procedures (this is documented).	• Obtaining a pain score before the infant has been prepared for the procedure does not give you the information you need: REASSESS—REASSESS—REASSESS
Role of the family	• Parent education regarding infant pain and stress is provided within the first week of hospital admission; learning is validated. • Parents are partners in pain and stress prevention, assessment, and management for their infant(s). • Parents are encouraged, empowered, and supported to advocate for and provide comfort to their hospitalized infant(s).	• Share your knowledge of pain and stress behaviors with parents—educate and empower them • Schedule painful procedures when the parents are present (all laboratories do not need to be drawn at 0400)
Activities of Daily Living		
Posture and mobility	• Optimal postural alignment that supports spontaneous movement during caregiving and at rest is a standard of care. • Infants receive appropriate therapeutic interventions aimed at optimizing neuromotor and neurobehavioral performance for improved short- and long-term outcomes. • Skin-to-skin care is the position of choice for eligible infants.	• Know how to effectively use your unit's postural aids and also when to remove them; they are not accessories to the infant's bed but are therapeutic supports • Support the infant's posture during all movements and caregiving (weights, transfer to a different bed, etc.)
Eating experiences	• Breast milk is actively recommended as the preferred diet for hospitalized infants. • Skin-to-skin care and prefeeding activities at the breast are actively encouraged and supported. • Bottle-feeding encounters are introduced no sooner than 34 weeks' gestational age based on the infant's feeding readiness behaviors; these behaviors direct all bottle-feeding experiences.	• Educate yourself on the current best practices in infant feeding • Be an advocate for improved eating experiences for the patients you serve—role-model infant-driven feeding • Ensure the first oral feeding for breastfeeding dyads occurs at the breast
Skin Care and Hygiene	• Skin and mucous membrane integrity is routinely assessed (at least daily) using a validated, reliable tool • Recommended bathing frequency (sponge, tub, swaddled) is no more than 3 times/week for the purpose of removing debris and general hygiene • Skin and mucous membranes are protected from potential secondary injury, transepidermal water losses and perturbations to the surface microbiome	• Know your unit's skin assessment tool and assess the entire surface of the skin and mucous membranes ensuring accurate documentation and the prompt reporting of abnormal findings • Remember that tub bathing is a parent activity; ensure that parents are confident and competent to perform this parenting activity • Protect infant skin from pressure points and adhesives; remove adhesives gently with non-toxic substances. Promote skin-to-skin care to stabilize the infant's microbiome
Family Collaborative Care		
Presence and partnership	• Parents have unrestricted access to their infant(s). • Parents are invited and encouraged to be present and participate in bedside rounds. • Supportive spaces and resources are readily available to include restrooms, comfortable seating, designated space for personal belongings, and other comfort resources that support parental presence.	• Parents are not visitors—be the champion who changes the language in your NICU • Authentically advocate for and encourage parents to participate in rounds and change of shift • Assess the resources available in your unit that can optimize the parent's experience and the parent's presence with the baby

(*continued*)

TABLE 34.5

THE CLINICIAN'S TOOLBOX FOR TRAUMA-INFORMED CARE PROVIDES THE READER WITH QUALITY CORE MEASURES, ATTRIBUTES, AND SUGGESTED NURSING ACTIONS (*continued*)

Family Collaborative Care		
Attribute	**Criteria**	**Nursing Actions**
Emotional well-being	• The unit has appropriate staffing ratios of licensed mental health professionals. • Parents are assessed/reassessed routinely for postpartum depression and acute stress disorder; all staff are competent and responsible for this assessment. • Appropriate, effective therapeutic interventions and additional crisis support resources are available to families and staff, including family support groups, a peer-to-peer support network, and other support resources (e.g., spiritual, financial).	• Talk with your unit-based social workers about how they support the family in crisis; brainstorm about additional resources to optimize parent emotional well-being • Start a family support group; connect with March of Dimes
Competence and confidence	• Competency-based education is provided to all parents across all facets of the core measures for age-appropriate care to include (but not limited to) breastfeeding skills, skin-to-skin care, safe sleep, bathing and hygiene practices, infant communication, nonpharmacologic pain and stress strategies, and so on. • All staff are culturally competent to support the parenting needs of their unique patient demographics. • Parents are empowered and supported in relationship building and role-validating activities with their infant(s) such as the provision of routine infant caregiving, feeding activities, supporting their infant during painful/stressful procedures, advocating for their infant(s), and so on.	• Develop a parent competency-based education program • Engage former NICU parents for input and assistance • Create a fun way of recognizing parent skill building

AAP, American Academy of Pediatrics.

Source: Adapted from Coughlin, M. (2016). *Trauma-informed care in the NICU: Evidence-based practice guidelines for neonatal clinicians.* New York, NY: Springer Publishing Company.

SAFETY AND QUALITY IN THE NICU—A CALL TO ACTION

"It is easier to build strong children than to repair broken men."
—Frederick Douglass (Rowland, 2014)

Quality and safety in the NICU begin with *you* choosing courage over comfort in your daily practice as a neonatal nursing professional—the courage to lead from the frontline and be the change you want to see in your NICU. It takes courage to resist and change the status quo, but that is what is needed to improve outcomes across the continuum of care for infants, families, and clinicians. The 2012 policy statement from the American Academy of Pediatrics (AAP; reaffirmed in 2016) urges all pediatric healthcare professionals to adopt an eco-biodevelopmental (EBD) framework as a means of understanding the determinants of lifelong health and wellness (Garner et al., 2012). The EBD framework explains how the social and physical environment of the developing individual impacts his or her biology and subsequently influences the developmental trajectory for health and wellness, both physically and mentally, over the life span (Shonkoff et al., 2012). The AAP urges educational institutions to prepare pediatric professionals to incorporate the growing body of knowledge regarding toxic stress and its deleterious effects on development into their curriculum (Garner et al., 2012). Finally, the AAP admonishes pediatric professionals (of which neonatology is a subspecialty) to be proactive educators of parents and families about toxic stress and the associated consequences. Being vocal advocates for the development and implementation of evidence-based interventions that reduce toxic stress and mitigate the adverse effects of early life adversity is crucial (Garner et al., 2012).

In advocating for the implementation of evidence-based best practices that reduce and mitigate toxic stress in the NICU, it is important to understand the environment of care and the complex dynamics that influence trauma-informed neuroprotective nursing. Workforce shortages, staffing levels, work intensification, and "bottom line" hospital cultures have been linked to an emerging epidemic of missed or unfinished nursing care (Ball, Murrells, Rafferty, Morrow, & Griffiths, 2014; Harvey et al., 2015; Harvey et al., 2016; Willis et al., 2015). Missed care or rationed care, defined as a failure to carry out necessary tasks due to inadequate time, staffing level, and/or skill mix, has been associated with deficiencies in the work environment and is a predictor of nursing job satisfaction, patient satisfaction, and patient outcomes (Ball et al., 2014; Kalisch, Landstrom, & Hinshaw, 2009; Papastavrou, Andreou, & Efstathiou, 2014; Papastavrou, Andreou, Tsangari, & Merkouris, 2014; Rochefort & Clarke, 2010). Physicians have also described the phenomenon of care rationing at the bedside and it creates a moral dilemma for many (Strech, Persad, Marckmann, & Danis, 2009).

In a comprehensive literature review of unfinished nursing care, missed care, and implicitly rationed care, Jones, Hamilton, and Murry (2015) uncover that between 55% and 95% of international nurses in acute care hospitals report leaving at least one task undone on their last shift worked and these errors by omission have a cumulative effect and leave vulnerable patients with unmet educational, emotional, physical and psychological needs. Tubbs-Cooley, Pickler, Younger, and Mark (2015) invited a random sample of regionally diverse certified neonatal nurses

TABLE 34.6

MISSED NICU NURSING CARES

1. Attendance at daily rounds	2. All vital information communicated to other staff during handoffs	3. Feedings offered when baby exhibits cues of hunger	4. Parents prepared for discharge	5. Baby repositioned at least once q2h
6. Oral care for ventilated babies provided per protocol	7. Emotional support provided to parents/ family	8. PRN meds given per order	9. Oxygen titrated per protocol/order	10. Pain managed using pharmacologic or supportive care approaches
11. Baby bathed routinely and/ or as needed	12. Baby received developmentally supportive care (skin-to-skin, nesting)	13. Central line site care and assessments per protocol	14. Documentation completed as care is provided	15. Peripheral intravenous site care and assessments per protocol
16. Parents included in baby's care	17. Critical laboratories/ vital sign values communicated to team per protocol	18. Intake and output monitored hourly or per protocol	19. Infection control precautions followed per protocol	20. Alarms responded to in a timely manner
21. Parents educated about home management of illness, including devices, medications, and general care of preterm infant	22. Skin and wound care provided routinely and/ or as needed	23. Pain assessed according to protocol	24. Laboratories/ specimens obtained as ordered	25. Hand hygiene per protocol
26. Medication effectiveness assessed in 30–60 minutes of administration or per protocol	27. Safety checks of bedside equipment completed once per shift or per protocol	28. Medications administered in 30 minutes of scheduled time	29. Vital signs assessed per protocol	30. Focused reassessments according to the baby's condition
31. Oral feed offered at each feeding opportunity (when infant cleared for PO)	32. Code readiness data assessed once per shift or per protocol	33. "6 rights" of medication administration adhered to each time a medication is given	34. Comprehensive physical assessments per protocol	35. High-risk medications verified per protocol

Source: Adapted from Stokowski, L. A. (2015). The missed list: Revelations of busy NICU nurses. *Medscape*. Retrieved from https://www.medscape.com/viewarticle/837631

who provided direct patient care in the NICU to participate in a descriptive study of missed care in the NICU using the MISSCARE Survey (Kalisch & Williams, 2009) adapted for use in neonatal intensive care. Of the nurses reporting, 52% missed at least 1 of 35 nursing care items on their last shift worked (Table 34.6).

Nursing care with the highest missed frequency included attendance in daily rounds, medication effectiveness reassessment, and oral feedings offered to infants who exhibited feeding readiness behaviors (Tubbs-Cooley et al., 2015). Rochefort and Clarke (2010) describe care activities most frequently rationed in the NICU to include discharge planning, parental support and teaching, and infant comfort care. Missed care creates a moral conundrum for the neonatal clinician who feels forced to prioritize and rationalize what is and is not completed during any given shift, minimizing the implications of the missed care, and adding a layer of professional frustration and disappointment in abandoning moral integrity and accountability.

> Missed care may not necessarily be an indicator of poor-quality nursing, but rather a by-product of rational nurse decision-making in the midst of competing priorities. (Tubbs-Cooley et al., 2015, p. 821)

The reported reasons for missed nursing care in the NICU included frequent interruptions, unexpected increase in patient volume or acuity, medications not available when needed, supplies/equipment not available, inadequate number of nurses, lack of protected time, lack of clerical/assistive personnel, inadequate handoff, and tension/communication breakdown across physicians, nurses, and/or other departments (Tubbs-Cooley et al., 2015). Other reasons for missed nursing care include multitasking, task switching, fatigue and physical exhaustion, moral distress and compassion fatigue, leadership issues, and complacency (Kalisch, 2015). Looking at missed nursing care through a trauma lens, we might conclude that many of these "reasons" for missed care may actually be linked to trauma exposure responses and a healthcare culture designed in the early 1900s where nursing was bundled into the cost of the bed and the board for any given hospital stay (Welton & Harper, 2016). This approach to quantifying and qualifying the value of nursing monumentally fails the patient and fails our profession. We are more than skilled technicians: we are healers who bear witness to the suffering of others. We walk with our patients when they

are most vulnerable, honoring their journey, comforting them, advocating for them.

Critically ill infants and their families are profoundly vulnerable to poor outcomes that negatively impact their short- and long-term health; reducing missed care for this unique patient population by improving care environments for patients and the professional practice milieu for clinicians is feasible and necessary (Lake et al., 2017). We know the quality of nursing makes a difference, but if we fail to capture and quantify it, then we will continue to fail our patients, be frustrated in our work, experience compassion fatigue, burn out, and leave the profession. The adage "if it is not documented, it is not done" rings true with the missed care phenomenon. If I am not required to document certain caregiving activities, then maybe they are not really that important and missing them frees me up to do other "higher priority" caregiving. But, this approach invalidates that part of nursing which is the heart and soul of caring for others. Using value-based metrics, Welton and Harper (2016) suggest focusing on the individual nurse as a provider of care and identifying the interaction or encounter of a nurse and a patient, family, or community. Value-oriented care metrics for the NICU must reflect a commitment to trauma-informed, patient- and family-centered care.

> "We can't keep adding to the nurse's workload and expect that everything will get done. Nurses are going to make decisions about what they can and can't accomplish, and this will often depend on what hospitals are holding them accountable for." . . . Do we want checks in all the right boxes, or do we want nurses to provide the care that patients need? (Stokowski, 2015, Viewpoint)

SUMMARY

Decisions about what can and cannot be accomplished are informed by the organizational and unit culture. If the culture is one that does not recognize the impact of trauma on the caregiver, not much will change. However, if we truly embrace the tenets of nursing it becomes incumbent on us, as nurses, to stand in our power, and change the current paradigm to one that is trauma-informed and neuroprotective of our patients, their families, and ourselves.

> Nursing is the protection, promotion, and optimization of health and abilities, prevention of illness and injury, facilitation of healing, alleviation of suffering through the diagnosis and treatment of human response, and advocacy in the care of individuals, families, groups, communities, and populations. (American Nurses Association, 2016)

ONLINE RESOURCES

Wahlin, K. (2015). *Utilizing trauma-informed care to strengthen your support organization*. San Francisco, CA: NICU Healing. Retrieved from http://www.nationalperinatal.org/resources/Documents/Utilizing%20Trauma-Informed%20Care%20to%20Strengthen%20Your%20Support%20Organization%20Final%20Powerpoint%202015.pdf

Wahlin, K. (2016). The benefits of trauma-informed care in the NICU. Retrieved from https://www.kevinmd.com/blog/2016/01/benefits-trauma-informed-care-nicu.html

REFERENCES

American Nurses Association. (2016). Nursing: Scope and standards of practice (3rd ed.). Bethesda, MD: Author.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing.

Ball, J. E., Murrells, T., Rafferty, A. M., Morrow, E., & Griffiths, P. (2014). "Care left undone" during nursing shifts: Associations with workload and perceived quality of care. *BMJ Quality & Safety, 23*(2), 116–125. doi:10.1136/bmjqs-2012-001767

Busse, M., Stromgren, K., Thorngate, L., & Thomas, K. A. (2013). Parents' responses to stress in the neonatal intensive care unit. *Critical Care Nurse, 33*(4), 52–59; quiz 60. doi:10.4037/ccn2013715

Carbajal, R., Rousset, A., Danan, C., Coquery, S., Nolent, P., Ducrocq, S., . . . Breart, G. (2008). Epidemiology and treatment of painful procedures in neonates in intensive care units. *Journal of the American Medical Association, 300*(1), 60–70. doi:10.1001/jama.300.1.60

Caring Essentials Collaborative. (2018). *Trauma-informed, neuroprotective care for hospitalized infants, families, and staff*. Retrieved from https://www.caringessentials.net

Centre, B. S. R. (2012). *When compassion hurts: Burnout, vicarious trauma and secondary trauma in prenatal and early childhood service providers*. Toronto, ON, Canada: Best Start Resource Centre.

Chau, V., Synnes, A., Grunau, R. E., Poskitt, K. J., Brant, R., & Miller, S. P. (2013). Abnormal brain maturation in preterm neonates associated with adverse developmental outcomes. *Neurology, 81*(24), 2082–2089. doi:10.1212/01.wnl.0000437298.43688.b9

Cheng, E. R., Kotelchuck, M., Gerstein, E. D., Taveras, E. M., & Poehlmann-Tynan, J. (2016). Postnatal depressive symptoms among mothers and fathers of infants born preterm: Prevalence and impacts on children's early cognitive function. *Journal of Developmental and Behavioral Pediatrics, 37*(1), 33–42. doi:10.1097/dbp.0000000000000233

Chernikova, D. A., Madan, J. C., Housman, M. L., Zain-ul-abideen, M., Lundgren, S. N., Morrison, H. G., . . . Hoen, A. G. (2018). The premature infant gut microbiome during the first 6 weeks of life differs based on gestational maturity at birth. *Pediatric Research, 84*, 71–79. doi:10.1038/s41390-018-0022-z

Coates, S. W. (2016). Can babies remember trauma? Symbolic forms of representation in traumatized infants. *Journal of the American Psychoanalytic Association*, *64*(4), 751–776. doi:10.1177/0003065116659443

Coughlin, M. (2011). *Age-appropriate care of the premature and critically ill hospitalized infant: Guideline for practice*. Glenview, IL: National Association of Neonatal Nurses.

Coughlin, M. (2014). *Transformative nursing in the NICU: Trauma-informed age-appropriate care*. New York, NY: Springer Publishing Company.

Coughlin, M. (2016). *Trauma-informed care in the NICU: Evidence-based practice guidelines for neonatal clinicians*. New York, NY: Springer Publishing Company.

Coughlin, M., Gibbins, S., & Hoath, S. (2009). Core measures for developmentally supportive care in neonatal intensive care units: Theory, precedence and practice. *Journal of Advanced Nursing, 65*(10), 2239–2248. doi:10.1111/j.1365-2648.2009.05052.x

D'Agata, A. L., Coughlin, M., & Sanders, M. R. (2018). Clinician perceptions of the NICU infant experience: Is the NICU hospitalization traumatic? *American Journal of Perinatology, 35*, 1159–1167. doi:10.1055/s-0038-1641747

D'Agata, A. L., Roberts, M. B., Ashmeade, T., Dutra, S. V. O., Kane, B., & Groer, M. (2019). Novel method of measuring chronic stress for preterm infants: Skin cortisol. *Psychoneuroendocrinology*, *102*, 204–211. doi:10.1016/j.psyneuen.2018.12.22

D'Agata, A. L., Walsh, S., Vittner, D., Cong, X., McGrath, J. M., & Young, E. E. (2017). FKBP5 genotype and early life stress exposure predict neurobehavioral outcomes for preterm infants. *Developmental Psychobiology, 59*, 410–418. doi:10.1002/dev.21507

D'Agata, A. L., Wu, J., Welandawe, M. K. V., Dutra, S. V. O., Kane, B., & Groer, M. (2019, ahead of print). Effects of Early Life NICU Stress on the Developing Gut Microbiome. *Developmental Psychobiology*. doi:10.1002/dev.21826

D'Agata, A. L., Young, E. E., Cong, X., Grasso, D. J., & McGrath, J. M. (2016). Infant medical trauma in the neonatal intensive care unit (IMTN): A proposed concept for science and practice. *Advances in Neonatal Care, 16*(4), 289–297. doi:10.1097/ANC.0000000000000309

Dahl, C., Stigum, H., Valeur, J., Iszatt, N., Lenters, V., Peddada, S., . . . Eggesbø, M. (2018). Preterm infants have distinct microbiomes not explained by mode of delivery, breastfeeding duration or antibiotic exposure. *International Journal of Epidemiology, 47*, 1658–1669. doi:10.1093/ije/dyy064

Dalia, C., Abbas, K., Colville, G., & Brierley, J. (2013). G49 Resilience, post-traumatic stress, burnout and coping in medical staff on the paediatric and neonatal intensive care unit (P/NICU)—A survey. *Archives of Disease in Childhood, 98*(Suppl. 1), A26. doi:10.1136/archdischild-2013-304107.061

Felitti, V. J., Anda, R. F., Nordenberg, D., Williamson, D. F., Spitz, A. M., Edwards, V., . . . Marks, J. S. (1998). Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults: The Adverse Childhood Experiences (ACE) study. *American Journal of Preventive Medicine, 14*(4), 245–258. doi:10.1016/S0749-3797(98)00017-8

Flacking, R., Lehtonen, L., Thomson, G., Axelin, A., Ahlqvist, S., Moran, V. H., . . . the Separation and Closeness Experiences in the Neonatal Environment Group. (2012). Closeness and separation in neonatal intensive care. *Acta Pædiatrica, 101*(10), 1032–1037. doi:10.1111/j.1651-2227.2012.02787.x

Garber, J. S., & Seligman, M. E. P. (1980). *Human helplessness: Theory and application*. San Diego, CA: Academic Press.

Garner, A. S., Shonkoff, J. P., Siegel, B. S., Dobbins, M. I., Earls, M. F., Garner, A. S., . . . Wood, D. L. (2012). Early childhood adversity, toxic stress, and the role of the pediatrician: Translating developmental science into lifelong health. *Pediatrics, 129*(1), e224. doi:10.1542/peds.2011-2662

Giarraputo, J., DeLoach, J., Padbury, J., Uzun, A., Marsit, C., Hawes, K., & Lester, B. (2017). Medical morbidities and DNA methylation of NR3C1 in preterm infants. *Pediatric Research, 81*(1-1), 68–74. doi:10.1038/pr.2016.185

Godoy, L. D., Rossignoli, M. T., Delfino-Pereira, P., Garcia-Cairasco, N., & de Lima Umeoka, E. H. (2018). A comprehensive overview on stress neurobiology: Basic concepts and clinical implications. *Frontiers in Behavioral Neuroscience, 12*, 127. doi:10.3389/fnbeh.2018.00127

Graham's Foundation. (2017). The invisible effects of premature birth. Retrieved from https://grahamsfoundation.org/invisible-effects-prematurity

Greene, M. M., Rossman, B., Patra, K., Kratovil, A. L., Janes, J. E., & Meier, P. P. (2015). Depressive, anxious and perinatal post-traumatic distress in mothers of very low birth weight infants in the NICU. *Journal of Developmental Behavioral Pediatrics, 36*(5), 362–370. doi:10.1097/DBP.0000000000000174

Grunau, R. E. (2013). Neonatal pain in very preterm infants: Long-term effects on brain, neurodevelopment and pain reactivity. *Rambam Maimonides Medical Journal, 4*(4), e0025. doi:10.5041/rmmj.10132

Grunau, R. E., Holsti, L., Haley, D. W., Oberlander, T., Weinberg, J., Solimano, A., … Yu, W. (2005). Neonatal procedural pain exposure predicts lower cortisol and behavioral reactivity in preterm infants in the NICU. *Pain*, *113*(3), 293–300.

Halifax, J. (2014). G.R.A.C.E. for nurses: Cultivating compassion in nurse/patient interactions. *Journal of Nursing Education and Practice, 4*(1), 121–128. doi:10.5430/jnep.v4n1p121

Harrison, W., & Goodman, D. (2015). Epidemiologic trends in neonatal intensive care, 2007–2012. *JAMA Pediatrics, 169*(9), 855–862. doi:10.1001/jamapediatrics.2015.1305

Harvey, C., Buckley, C., Forrest, R., Roberts, J., Searle, J., Meyer, A., & Thompson, S. (2015). Aberrant work environments, rationed care as system failure or missed care as skills failure? *Journal of Nursing and Health Care, 2*(1), 72–80. doi:10.5176/2345-718X_2.1.66

Harvey, C., Willis, E., Henderson, J., Hamilton, P., Toffoli, L., Verrall, C., . . . Abery, E. (2016). Priced to care: Factors underpinning missed care. *Journal of Industrial Relations, 58*(4), 510–526. doi:10.1177/0022185616638096

Holsti, L., Gruanu, R. E., Oberlander, T. F., & Whitfield, M. R. (2005). Prior pain induces heightened motor responses during clustered care in preterm infants in the NICU. *Early Human Development*, *81*(3), 293–302.

Holsti, L., Grunau, R. E., Whitfiled, M. F., Oberlander, T. F., & Lindh, V. (2006). Behavioral responses to pain are heightened after clustered care in preterm infants born between 30 and 32 weeks gestational age. *The Clinical Journal of Pain, 22*(9), 757–764.

Johnson, S. B., Riley, A. W., Granger, D. A., & Riis, J. (2013). The science of early life toxic stress for pediatric practice and advocacy. *Pediatrics, 131*(2), 319–327. doi:10.1542/peds.2012-0469

Jones, T. L., Hamilton, P., & Murry, N. (2015). Unfinished nursing care, missed care, and implicitly rationed care: State of the science review. *International Journal of Nursing Studies, 52*(6), 1121–1137. doi:10.1016/j.ijnurstu.2015.02.012

Kalisch, B. J. (2015). *Errors of omission: How missed nursing care imperils patients*. Silver Spring, MD: American Nurses Association.

Kalisch, B. J., Landstrom, G. L., & Hinshaw, A. S. (2009). Missed nursing care: A concept analysis. *Journal of Advanced Nursing, 65*(7), 1509–1517. doi:10.1111/j.1365-2648.2009.05027.x

Kalisch, B. J., & Williams, R. A. (2009). Development and psychometric testing of a tool to measure missed nursing care. *Journal of Nursing Administration, 39*(5), 211–219. doi:10.1097/NNA.0b013e3181a23cf5

Keene, E. A., Hutton, N., Hall, B., & Rushton, C. (2010). Bereavement debriefing sessions: An intervention to support health care professionals in managing their grief after the death of a patient. *Pediatric Nursing, 36*(4), 185–189; quiz 190. Retrieved from https://www.pediatricnursing.net/issues/10julaug/abstr1.html

Kersting, A., Dorsch, M., Wesselmann, U., Ludorff, K., Witthaut, J., Ohrmann, P., . . . Arolt, V. (2004). Maternal posttraumatic stress response after the birth of a very low-birth-weight infant. *Journal of Psychosomatic Research, 57*(5), 473–476. doi:10.1016/j.jpsychores.2004.03.011

Lake, E. T., de Cordova, P. B., Barton, S., Singh, S., Agosto, P. D., Ely, B., . . . Aiken, L. H. (2017). Missed nursing care in pediatrics. *Hospital Pediatrics, 7*(7), 378–384. doi:10.1542/hpeds.2016-0141

Lasiuk, G. C., Comeau, T., & Newburn-Cook, C. (2013). Unexpected: An interpretive description of parental traumas' associated with preterm birth. *BMC Pregnancy Childbirth, 13*(1), s13. doi:10.1186/1471-2393-13-S1-S13

Lefkowitz, D. S., Baxt, C., & Evans, J. R. (2010). Prevalence and correlates of posttraumatic stress and postpartum depression in parents of infants in the neonatal intensive care unit (NICU). *Journal of Clinical Psychology in Medical Settings, 17*(3), 230–237. doi:10.1007/s10880-010-9202-7

Lipsky, L. D. (2009). *Trauma stewardship: An everyday guide to caring for self while caring for others*. San Francisco, CA: Berrett-Koehler Publishers.

McEwen, B. S. (2004). Protection and damage from acute and chronic stress: Allostasis and allostatic overload and relevance to the pathophysiology of psychiatric disorders. *Annals of the New York Academy of Sciences, 1032*, 1–7. doi:10.1196/annals.1314.001

McEwen, B. S. (2007). Physiology and neurobiology of stress and adaptation: Central role of the brain. *Physiological Reviews, 87*(3), 873–904. doi:10.1152/physrev.00041.2006

McGrath, M. M., Sullivan, M. C., Lester, B. M., & Oh, W. (2000). Longitudinal neurologic follow-up in neonatal intensive care unit survivors with various neonatal morbidities. *Pediatrics, 106*(6), 1397–1405. doi:10.1542/peds.106.6.1397

Milette, I., Martel, M.-J., da Silva, M. R., & Coughlin McNeil, M. (2017a). Guidelines for the institutional implementation of developmental neuroprotective care in the neonatal intensive care unit. Part A: Background and rationale. A joint position statement from the CANN, CAPWHN, NANN, and COINN. *Canadian Journal of Nursing Research, 49*(2), 46–62. doi:10.1177/0844562117706882

Milette, I., Martel, M.-J., da Silva, M. R., & Coughlin McNeil, M. (2017b). Guidelines for the institutional implementation of developmental neuroprotective care in the NICU. Part B: Recommendations and justification. A joint position statement from the CANN, CAPWHN, NANN, and COINN. *Canadian Journal of Nursing Research, 49*(2), 63–74. doi:10.1177/0844562117708126

Miller, R. J., Sullivan, M. C., Hawes, K., & Marks, A. K. (2009). The effects of perinatal morbidity and environmental factors on health

status of preterm children at age 12. *Journal of Pediatric Nursing, 24*(2), 101–114. doi:10.1016/j.pedn.2008.02.031

Montirosso, R., Del Prete, A., Bellù, R., Tronick, E., Borgatti, R., & the Neonatal Adequate Care for Quality of Life Study Group. (2012). Level of NICU quality of developmental care and neurobehavioral performance in very preterm infants. *Pediatrics, 129*(5), e1129–e1137. doi:10.1542/peds.2011-0813

Montirosso, R., Provenzi, L., Fumagalli, M., Sirgiovanni, I., Giorda, R., Pozzoli, U., . . . Borgatti, R. (2016). Serotonin transporter gene (SLC6A4) methylation associates with neonatal intensive care unit stay and 3-month-old temperament in preterm infants. *Child Development, 87*(1), 38–48. doi:10.1111/cdev.12492

Montirosso, R., Tronick, E., & Borgatti, R. (2016). Promoting neuroprotective care in neonatal intensive care units and preterm infant development: Insights from the neonatal adequate care for quality of life study. *Child Development Perspectives, 11*(1), 9–15. doi:10.1111/cdep.12208

Moore, T. A., & Pickler, R. H. (2017). Feeding intolerance, inflammation, and neurobehaviors in preterm infants. *Journal of Neonatalogy Nursing, 23*(3), 134–141. doi:10.1016/j.jnn.2016.09.009

Moore, T. A., Wilson, M. E., Schmid, K. K., Anderson-Berry, A., French, J. A., & Berger, A. M. (2013). Relations between feeding intolerance and stress biomarkers in preterm infants. *Journal of Pediatric Gastroenterol and Nutrition, 57*(3), 356–362. doi:10.1097/MPG.0b013e3182953093

Naef, R. (2006). Bearing witness: A moral way of engaging in the nurse–person relationship. *Nursing Philosophy, 7*(3), 146–156. doi:10.1111/j.1466-769X.2006.00271.x

Newnham, C. A., Inder, T. E., & Milgrom, J. (2009). Measuring preterm cumulative stressors within the NICU: The neonatal infant stressor scale. *Early Human Development, 85*(9), 549–555. doi:10.1016/j.earlhumdev.2009.05.002

Nightingale, F. (1860). *Notes on nursing: What it is and what it is not*. Mineola, NY: Dover Publications.

Papastavrou, E., Andreou, P., & Efstathiou, G. (2014). Rationing of nursing care and nurse–patient outcomes: A systematic review of quantitative studies. *The International Journal of Health Planning and Management, 29*(1), 3–25. doi:10.1002/hpm.2160

Papastavrou, E., Andreou, P., Tsangari, H., & Merkouris, A. (2014). Linking patient satisfaction with nursing care: The case of care rationing—A correlational study. *BMC Nursing, 13*(1), 26. doi:10.1186/1472-6955-13-26

Ranger, M., Zwicker, J. G., Chau, C. M., Park, M. T., Chakravarthy, M. M., . . . Grunau, R. E. (2015). Neonatal pain and infection relate to smaller cerebellum in very preterm children at school age. *Journal of Pediatrics, 167*(2), 292–298.e1. doi:10.1016/j.jpeds.2015.04.055

Remen, N. R. (1996). *Kitchen table wisdom: Stories that heal*. New York, NY: Riverhead Books.

Rochefort, C. M., & Clarke, S. P. (2010). Nurses' work environments, care rationing, job outcomes, and quality of care on neonatal units. *Journal of Advanced Nursing, 66*(10), 2213–2224. doi:10.1111/j.1365-2648.2010.05376.x

Roque, A. T. F., Lasiuk, G. C., Radunz, V., & Hegadoren, K. (2017). Scoping review of the mental health of parents of infants in the NICU. *Journal of Obstetric, Gynecologic, and Neonatal Nursing*, *46*(4), 576–587. doi:10.1016/j.jogn.2017.02.005

Rowland, A. (2014). It is easier to build strong children than to repair broken men. Retrieved from https://drandrewrowland.wordpress.com/2014/04/25/it-is-easier-to-build-strong-children-than-to-repair-broken-men-frederick-douglass-1817-1895

Sanders, M. R., & Hall, S. L. (2018). Trauma-informed care in the newborn intensive care unit: Promoting safety, security and connectedness. *Journal of Perinatology, 38*(1), 3–10. doi:10.1038/jp.2017.124

Shaw, R. J., Bernard, R. S., Deblois, T., Ikuta, L. M., Ginzburg, K., & Koopman, C. (2009). The relationship between acute stress disorder and posttraumatic stress disorder in the neonatal intensive care unit. *Psychosomatics, 50*(2), 131–137. doi:10.1176/appi.psy.50.2.131

Shonkoff, J. P., Garner, A. S., The Committee on Psychosocial Aspects of Child and Family Health, Committee on Early Childhood, Adoption, and Dependent Care, and Section on Developmental and Behavioral Pediatrics, Siegel, B. S., . . . Wood, D. L. (2012). The lifelong effects of early childhood adversity and toxic stress. *Pediatrics, 129*(1), e232. doi:10.1542/peds.2011-2663

Smith, G. C., Gutovich, J., Smyser, C., Pineda, R., Newnham, C., Tjoeng, T. H., . . . Inder, T. (2011). NICU stress is associated with brain development in preterm infants. *Annals of Neurology, 70*(4), 541–549. doi:10.1002/ana.22545

Stokowski, L. A. (2015). The missed list: Revelations of busy NICU nurses. *Medscape*. Retrieved from http://www.medscape.com/viewarticle/837631

Strech, D., Persad, G., Marckmann, G., & Danis, M. (2009). Are physicians willing to ration health care? Conflicting findings in a systematic review of survey research. *Health Policy, 90*(2/3), 113–124. doi:10.1016/j.healthpol.2008.10.013

Substance Abuse and Mental Health Services Administration. (2014). *SAMHSA's concept of trauma and guidance for a trauma-informed approach*. Rockville, MD: Author.

Sullivan, M. C., Msall, M. E., & Miller, R. J. (2012). 17-year outcome of preterm infants with diverse neonatal morbidities: Part 1—Impact on physical, neurological, and psychological health status. *Journal of Specialistics in Pediatric Nursing, 17*(3), 226–241. doi:10.1111/j.1744-6155.2012.00337.x

Tahirkheli, N. N., Cherry, A. S., Tackett, A. P., McCaffree, M. A., & Gillaspy, S. R. (2014). Postpartum depression on the neonatal intensive care unit: Current perspectives. *International Journal of Women's Health, 6*, 975–987. doi:10.2147/IJWH.S54666

Torowicz, D., Lisanti, A. J., Rim, J.-S., & Medoff-Cooper, B. (2012). A developmental care framework for a cardiac intensive care unit: A paradigm shift. *Advances in Neonatal Care, 12*(5S), S28–S32. doi:10.1097/ANC.0b013e318265aeef

Tubbs-Cooley, H. L., Pickler, R., Younger, J. B., & Mark, B. A. (2015). A descriptive study of nurse-reported missed care in neonatal intensive care units. *Journal of Advanced Nursing, 71*(4), 813–824. doi:10.1111/jan.12578

Van Der Kolk, B. (2014). *The body keeps the score: Brain, mind and body in the healing of trauma*. New York, NY: Penguin Group.

Vinall, J. & Grunau, R. E. (2014). Impact of repeated procedural pain-related stress in infants born very preterm. *Pediatric Research*, *75*(5), 584–587. doi:10.1038/pr.2014.16

Vittner, D., McGrath, J., Robinson, J., Lawhon, G., Cusson, R., Eisenfeld, L., . . . Cong, X. (2017). Increase in oxytocin from skin-to-skin contact enhances development of parent–infant relationship. *Biological Research for Nursing, 20*(1), 54–62. doi:10.1177/1099800417735633

Watson, J. (2018). *Unitary caring science: The philosophy and praxis of nursing*. Louisville: University Press of Colorado.

Welch, M. G., Firestein, M. R., Austin, J., Hane, A. A., Stark, R. I., Hofer, M. A., . . . Myers, M. M. (2015). Family nurture intervention in the neonatal intensive care unit improves social-relatedness, attention, and neurodevelopment of preterm infants at 18 months in a randomized controlled trial. *Journal of Child Psychology and Psychiatry, and Allied Disciplines, 56*(11), 1202–1211. doi:10.1111/jcpp.12405

Welch, M. G., Halperin, M. S., Austin, J., Stark, R. I., Hofer, M. A., Hane, A. A., & Myers, M. M. (2016). Depression and anxiety symptoms of mothers of preterm infants are decreased at 4 months corrected age with Family Nurture Intervention in the NICU. *Archives of Women's Mental Health, 19*(1), 51–61. doi:10.1007/s00737-015-0502-7

Welton, J. M., & Harper, E. M. (2016). Measuring nursing care value. *Nursing Economics, 34*(1), 7–14; quiz 15.

Whitfield, M. F. & Grunau, R. E. (2000). Behavior, pain perception, and the extremely low-birth-weight survivor. *Clinics in Perinatology*, *27*(2), 363–379.

Willis, E., Henderson, J., Hamilton, P., Toffoli, L., Blackman, I., Couzner, L., & Verrall, C. (2015). Work intensification as missed care. *Labour & Industry, 25*(2), 118–133. doi:10.1080/10301763.2015.1060811

Winchester, S. B., Sullivan, M. C., Roberts, M. B., & Granger, D. A. (2016). Prematurity, birth weight, and socioeconomic status are linked to atypical diurnal hypothalamic-pituitary-adrenal axis activity in young adults. *Research in Nursing & Health, 39*(1), 15–29. doi:10.1002/nur.21707

CHAPTER 35

Family: Essential Partner in Care

Jacqueline M. McGrath and Dorothy Vittner

INTRODUCTION

Parents are essential caregivers for their infants. While admission to the NICU may temporarily shift some of those caregiving responsibilities, it does not negate the importance of a parent's life-long role in their child's overall health and development (Niela-Vilén, Feeley, & Axelin, 2017). Current evidence is increasingly providing direction for how best to fully engage parents in the NICU. These opportunities include increasing both physical and emotional closeness within parent–infant interactions and caregiving activities as well as within caregiving, decision making, and management (Dykes, Thompson, Gardner, Moran, & Flacking, 2016; Flacking, Thomson, & Axelin, 2016; Niela-Vilén et al., 2017). Parent engagement is defined as a dynamic process focused on enhancing and supporting the parent–infant experience, specifically enhancing the acquisition of skills for problem-solving and provision of appropriate infant care based on the infant's unique needs at a particular point in time (Drenkard, 2014; Samra et al., 2013, 2015).

The premise of this concept is that with support from the nursing and medical team and through a parent's self-motivation to set goals and to utilize informational resources about the unique care necessary for their child, parents can increase their engagement while simultaneously improving the progression of their infant's health (Makris, Vittner, Samra, & McGrath, 2019; Provenzi, Barello, & Graffigna, 2015). Defining parent engagement facilitates identification of parent risks and needs for intervention to optimize outcomes for premature infants (Vittner et al., 2019). In the adult literature, patient activation is an evidence-based outcome of increased involvement in care (Greene & Hibbard, 2012; Hibbard & Greene, 2013). Supporting and facilitating parent engagement is one means of decreasing what has been recently documented as posttraumatic stress disorder (PTSD) experienced by parents who must traverse the unfamiliar and chaotic NICU environment in partnership with their high-risk infant (Garfield, Simon, Rutsohn, & Lee, 2018; Karatzias, Chouliara, Maxton, Freer, & Power, 2007; Santos, Yang, Docherty, White-Traut, & Holditch-Davis, 2016). The NICU environment has been repeatedly documented as traumatic to parents, and parents need increasing support depending on their reactions to the environment. Increasing parent engagement has the potential to enhance parent confidence, competence, and self-efficacy, which ultimately has potential to increase their ability to self-manage their child's care after discharge to optimize the health and developmental outcomes for the child (Amin, Tam, & Shorey, 2018; Vance & Brandon, 2017; Wittkowski, Garrett, Calam, & Weisberg, 2017). Even more importantly, the unique needs of the infant's developing brain demand that caregiving delivered by both parents and health providers be neuroprotective, matching the "expectations" for experiences that "nurture" their short- and long-term neurocognitive development (Bonnier, 2008; McGrath, 2008, 2013; McGrath, Cone, & Samra, 2011; Samra, McGrath, Wehbe, & Clapper, 2012). Trauma-informed care has been increasingly implicated in caregiving in the NICU, and we as caregivers need to continue to acknowledge that care is traumatic to all involved (D'Agata, Coughlin, & Sanders, 2018; Sanders & Hall, 2017).

Baum et al. reported how mothers who gave birth prematurely felt "somewhere between being pregnant and being a mother" and that this disconnect further added to their inability to reconnect and attach to their infant in the unfamiliar environment of the NICU (Baum, Weidberg, Osher, & Kohelet, 2012). These ambivalent feelings decrease the mother's ability to be appropriately responsive and sensitive to her infant's needs and potentially leads to dyssynchrony within mother–infant interactions and overall poorer attachment (Baker & McGrath, 2011; Flacking et al., 2016; Green, Darbyshire, Adams, & Jackson, 2015). Sometimes prenatal diagnosis provides the opportunity to enter and learn about the environment of the NICU prior to the birth of a high-risk infant. Although providing this information to families is helpful, if the birth is traumatic the context for what information the parents were provided prior to the birth may be lost (Beck, 2011).

Regardless of how a family enters the NICU, it is important to remember at that initial moment a partnership must be formed between the family and professionals providing care for the infant (Johnson et al., 2008; Reis, Rempel, Scott, Brady-Fryer, & van Aerde, 2010). This relationship must continue as a true collaborative partnership for as long as it is in the best interest of the child (Boykova & Kenner, 2010; Johnson et al., 2008). Even with the added focus on the integration of family-centered care (FCC) that is prevalent in most NICUs today, families continue to report being extremely distressed by the environment and their inability to parent their child in the way they had planned or the way they would at home (Baum et al., 2012; Santos et al., 2016; Stremler, Haddad, Pullenayegum, & Parshuram, 2017).

Partnerships exist when there is a relationship between two or more parties with a shared goal. Effective partnerships between

professionals and families are based on mutual respect, valuing of family expertise, fully shared information, and joint decision making (Johnson et al., 2008). When parents are consistently well informed and involved as partners within the NICU team, ethical dilemmas can be potentially lessened and care decisions optimized in the best interest of the infant and the family (Boykova & Kenner, 2010; Institute for Patient- and Family-Centered Care [IPFCC], 2013b). Partnership and true collaboration between families and health professionals are essential and form the crux of caregiving interventions discussed within this chapter.

Change is the most certain event throughout a person's life. A family experiencing the birth of an infant faces many changes. Some variations in lifestyle occur in the areas of employment, financial security, daily activities, relationships with others, and roles within the family. These changes have a major impact on each parent, family member, and on the family as a whole. When medical needs require admission of the infant to an intensive care nursery, the changes become even more significant because, for the most part, the complex needs of this unique infant or complicated birth have not been planned for or expected (Baum et al., 2012). For the family, these changes can be devastating and challenging. The more fully integrated the family is within the NICU caregiving team, the more unlikely will events be challenging. During this difficult time parents need more than support; they need to be true partners and an integral part of the process of caring for and parenting their child (Boykova & Kenner, 2010; Johnson et al., 2008; McGrath, 2007a). In the environment of the NICU, it is wholly impossible to provide excellent care to the infant without partnering with the parents or family, or preferably both, in every aspect of care (Agency for Healthcare Research and Quality, 2013; Boykova & Kenner, 2010; Stevens, Helseth, & Kurtz, 2010).

Families provide the foundation for health concepts and are the child's portal to the healthcare system. Family beliefs and individual health values are highly correlated. Families are the constant for the child. The provision of individualized developmental care (IDC), of which FCC is a core principle, is pivotal to optimize long-term medical and developmental outcomes for the child (Craig et al., 2015; Montirosso et al., 2012). The effects of IDC are documented into school age, adolescence, and young adulthood (Ekeus, Lindström, Lindblad, Rasmussen, & Hjern, 2010; McAnulty et al., 2013). For these reasons, understanding the many influences of the context of family on the mental health status of each of its members is important for those caring for infants and children (Beck, 2011; D'Agata et al., 2017; Garfield et al., 2018; Hall et al., 2015; Szaniecki & Barnes, 2016; Box 35.1). Most professionals collaborating with children and families believe that a family-centered approach is the best option, because this type of care supports optimal outcomes for the child in concert with those derived from high-quality professional and technical care (Craig et al., 2015; Institute for Patient and Family Centered Care [IPFCC], 2010b; Kersten-Alvarez, Hossman, Riksen-Walraven, Van Doesum, & Hoefnagels, 2011). Fundamental to the infant's developmental trajectory is early parent–infant contact. Parental–infant contact through nurturing touch, especially during skin-to-skin contact (SSC), has the potential to reduce the adverse consequences of critically ill infants (Kamphorst et al., 2018; Olsson, Eriksson, & Anderzen-Carlsson, 2017). These benefits are thought to occur though physiological changes in the infant and parents which facilitate increased feelings of comfort, attachment, and physiological stability (Campbell-Yeo et al., 2017; Casio, Moore, & McGlone, 2018; Mori, Khanna, Pledge, & Nakayama, 2010). SSC is an evidence-based holding strategy that increases the opportunity for parental proximity and provides a continuous interactive environment known to enhance infant physiological stability and affective closeness within the parent–infant dyad (Boundy et al., 2016; Cho et al., 2016; Feeley, Genest, Niela-Vilén, Charbonneau, & Axelin, 2016; Ludington-Hoe, 2011; Mori et al., 2010; Vittner et al., 2018, 2019).

Clear definitions of family and the philosophy of FCC are critical to the foundation of the concepts presented in this chapter. Role theory is used to explain the issues families face during this challenging time. Factors that influence parenting behaviors include personal experiences, medical and nursing staff expectations, environmental conditions, and peer relationships. These factors can either promote or interfere with the development of an intact family unit (Morey & Gregory, 2012; Reis et al., 2010). The birth of a critically ill newborn complicates the attachment process (Brooks, Rowley, Broadbent, & Petrie, 2012; Udry-Jørgennsen et al., 2011) as well as the learning of parenting skills, and thus, an evidence-based framework is provided for understanding what

Box 35.1

FUNDAMENTAL CHARACTERISTICS OF FAMILY-CENTERED CARE

The practice of FCC involves the following:

1. Recognizing the family as the constant in a child's life, whereas the service systems and those who work within each are always changing.
2. Facilitating family–professional partnerships and collaborations at all levels of healthcare provision.
3. Providing care for the individual child and his or her unique characteristics.
4. Families partnering and participating in program development, implementation, and evaluation.
5. Collaboration with families to contribute to policy formation.
6. Honoring the racial, ethnic, cultural, religious, and socioeconomic diversity of families.
7. Recognizing family strengths and individuality and celebrating those differences as valuable.
8. Respecting and supporting different methods of family coping with difficult situations and information.
9. Partnering and sharing with families, on a continuing basis and in a supportive manner, complete and unbiased information.
10. Encouraging and facilitating family-to-family support and networking.
11. Understanding and incorporating the developmental needs of infants, children, and their families into healthcare systems.
12. Implementing comprehensive policies and programs that provide emotional and financial support to meet the unique needs of families.
13. Designing accessible healthcare systems that are flexible, culturally competent, and responsive to family-identified needs.

Sources: Adapted from Johnson, B., Abraham, M., Conway, J., Simmons, L., Edgman-Levitan, S., Sodomka, P., . . . Ford, D. (2008). *Partnering with patients and families to design a patient- and family-centered health care system: Recommendations and promising practices*. Bethesda, MD: Institute for Family-Centered Care and Institute for Healthcare Improvement; Institute for Patient- and Family-Centered Care. (2017). *Advancing the practice of patient- and family-centered care in hospitals: How to get started*. Bethesda, MD: Author. Retrieved from http://www.ipfcc.org/resources/getting_started.pdf

families need in terms of true support in the neonatal setting. Several different models of family-centered care are presented. The chapter concludes with evidence-based FCC strategies that support optimal family functioning during the NICU experience and promote the discharge of intact families as the crisis of newborn intensive care begins to resolve. These strategies also include issues related to sibling adaptation and involvement of extended family members in the care and decision making related to the infant.

FAMILY-CENTERED CARE

FCC is a philosophy of care in which the pivotal role of the family in the lives of children is recognized and respected (IPFCC, 2017; Johnson et al., 2008). According to this philosophy, families are supported in their natural caregiving and decision-making roles by building on their unique strengths as persons and then extending this same examination of strengths to the family unit. FCC recognizes and promotes the normal patterns of a family's life at home and in the community. Rather than expecting the family to take on the medical culture of the institution, healthcare professionals recognize and reinforce the family's culture through a partnership formed in the best interests of the child. Parents and professionals are equals in a partnership committed to the child and to the development of optimum quality in the delivery of all levels of healthcare (IPFCC, 2013b, 2017). FCC strengthens the family unit through empowerment and advocacy by enabling the family to nurture and support their child's development (IPFCC, 2013b; Lee, Carter, Stevenson, & Harrison, 2014; Box 35.2).

From the child's perspective, FCC is safe and familiar; the infant/child is first and foremost a member of a family and care that is individualized to the family is also individualized to the infant (Hill, Knafl, & Santacroce, 2018). When the framework of FCC is the foundation for caregiving, the family is visible, available, and supportive of their infant's needs. They are an integral part of every decision that affects their child, even if they are not present at the bedside 24 hours a day like any other member of the health professional team (Craig et al., 2015; Miyagishima, Himuro, Kozuka, Mori, & Tsutsumi, 2017). Thus, their presence is noted in all aspects of care. The family members are empowered partners in the caregiving practices of their child within the healthcare setting (Johnson et al., 2008; McGrath, 2011). FCC begins wherever and whenever a family enters the healthcare system and continues throughout the hospitalization to discharge. Families should encounter this philosophy of care before birth in antenatal care, and continue it into the delivery room and beyond into the postpartum period (Hodnett, Gates, Hofmeyr, Sakala, & Weston, 2011; Lindner & McGrath, 2012). It is important to remember that families are not replaceable at any level in the overall development of the child. Within implementation of the philosophy of FCC, their impact always supersedes that of the healthcare system (Foster, Whitehead, Arabiat, & Frost, 2018; Gooding et al., 2011).

It is important to organize care to minimize the separation of parents and infant and to provide expertise in bonding and attachment theory that supports parents directly or indirectly. Nonseparation of infant and parents also has ethical and legal support. The United Nations Convention on the Rights of the Child from 1989 states in article 7: "The child . . . shall have the right from birth to . . . be cared for by his or her parents" and in article 9: "Parties shall ensure that a child shall not be separated from his or her parents against their will.. . ." Couplet care is an emerging concept within neonatal care that provides facilities for parents to live in the neonatal intensive care nursery along with their infants throughout the hospitalization by coupling the care of the infant with the care of the newly delivered mother. This model has been practiced in Sweden for over 10 years. It includes not only postpartum care after a normal delivery but also care of mothers with more advanced needs. After the immediate postpartum period, approximately half of all mothers with infants born prematurely have a prolonged need for medical care and would otherwise be separated from their infants during the very important first days of bonding and attachment (Westrup, 2015). When introducing couplet care, it is important to appropriately adjust the design and structure of the nursery. It is essential to build structures for a close collaboration with obstetrics since they must still have the medical responsibility for the mothers; for example, do rounds and prescribe medications and decide if the mother is receiving adequate care. FCC cannot happen in a vacuum; it must be supported by organizational policies and procedures that optimize the strengths of the family (Milette, Martel, Ribeiro da Silva, & Coughlin, 2017a, 2017b). Delivery requires a whole team approach where everyone has the same beliefs and attitudes toward the importance of families to ensure that *all* families receive this type of care.

Box 35.2

FOUNDATIONAL PRINCIPLES OF FAMILY-CENTERED CARE

- **Enabling:** Building on family strengths to create opportunities and ways for families to use the abilities and competencies they already have to learn new ones to meet child and family needs
- **Empowering:** Acknowledging and respecting the fact that families have existing strengths and capabilities and building on those strengths by supporting the family in meaningful decision making about issues that affect their welfare. Professionals who empower families interact and form partnerships with families in ways such that the family develops and maintains a sense of control over their own lives and are able to make positive changes to reinforce their own strengths, abilities, and actions.

Sources: Adapted from Johnson, B., Abraham, M., Conway, J., Simmons, L., Edgman-Levitan, S., Sodomka, P., . . . Ford, D. (2008). *Partnering with patients and families to design a patient- and family-centered health care system: Recommendations and promising practices*. Bethesda, MD: Institute for Family-Centered Care and Institute for Healthcare Improvement; Institute for Patient- and Family-Centered Care. (2017). *Advancing the practice of patient- and family-centered care in hospitals: How to get started*. Bethesda, MD: Author. Retrieved from http://www.ipfcc.org/resources/getting_started.pdf

DEFINITION OF FAMILY

The concept of who and what comprises a family in North America is defined best by each specific family unit. Families expand, contract, and realign at a rapid pace to keep up with the rapidly changing demands of our world. Today, dual-career families; single-parent households; unmarried couples; lesbian, gay, bisexual, queer, and transgender (LGBQT) couples; remarried couples; and sole-parent adoptions are all accepted models of family, in addition to the "traditional" family units common a century ago.

"Family" is a broad term that is best defined by the individual; however, in general, a family is made up of those people, both related and unrelated, who provide support, structure beliefs, and define values. Family has also been defined as a social system composed of two or more people who coexist in the context of expectations of reciprocal affection, mutual responsibility, and

temporal duration (Kaakinen, Gedaly-Duff, Hanson, & Coehlo, 2009). Families provide the framework through which individuals enter and interact with society at large. For infants and children, families are the means to resources, education, and society. Again, it is important to remember that families bring their children to the healthcare system for care. No matter how an infant comes to us, it comes with a family.

A family is defined by its members; "family" is an internal concept of how that particular group defines itself. It may be composed of blood relations or friends; it may not depend on a blood bond but on the emotional tie or closeness felt among its members. It also may be an extended family that includes parents, grandparents, other relatives, and friends. Families today are not necessarily defined as they have been in the past and not according to gender-specific roles. Families also can be defined by considering the degree to which the following five attributes are present (these attributes also depend on the family's societal and cultural orientation; Kaakinen et al., 2009).

1. A family is a social system or unit.
2. Family members may or may not be related by birth, adoption, or marriage.
3. A family may or may not include dependent children.
4. Families involve commitment and attachment.
5. Family members usually have roles and caregiving functions (e.g., protection, nourishment, and socialization).

ROLE THEORY

In the context of better understanding family dynamics, it is important to also review and examine role theory. Role theory, which first appeared in the literature in the 1930s, offers a framework for understanding families and identifying the roles that individuals play within the family. As a broad term, role theory represents a collection of concepts, subtheories, and research that address aspects of social behavior relevant to families. Roles are social contexts with patterned behaviors that develop over time and are predetermined by social forces. Roles are dynamic, interactional, and reciprocal relationships among individuals; therefore, values, attitudes, and behaviors influence these relationships. Each role has specific behaviors and expectations placed on it by society and these expectations guide individuals as to when, where, and in what manner they are to perform within the role.

Each role within a family has specific demands. An individual learns these demands by maturing and advancing through the middle to later stages of the life cycle: (a) adolescence, (b) adulthood, (c) marriage and parenthood, and (d) middle and old age. Individuals respond to the demands of a role differently based on their maturity and current developmental stage in the life cycle. For example, a single, adolescent girl would be expected to perform the maternal role differently from a married, adult woman.

Within role theory, seven areas of distress have been identified: (1) role ambiguity, (2) role conflict, (3) role incongruity, (4) role overload, (5) role underload, (6) role overqualification, and (7) role underqualification. These terms are defined in Table 35.1. Distress is often responsible for producing role stress and strain. Role stress is defined as either internal or external pressure that generates role strain. As a consequence, feelings of frustration, tension, or anxiety are produced in either the individual or the reciprocal partners. When problems occur within a role, or a person, the members of the group may need to modify or completely change roles. Changing roles can be stressful for the individual and the group. However, not changing roles can result in intrapersonal and interpersonal role conflict, which can lead to further stress and anxiety. Parenting in the NICU can lead to role conflict since parents may feel they are not the ones parenting their child (Curley, Hunsberger, & Harris, 2013; Treyvaud et al., 2011).

TABLE 35.1

POTENTIAL ROLE PROBLEMS

Role	Potential Problems
Ambiguity	Role expectations are vague or lack clarity.
Conflict	Role expectations are incompatible (conflicts exist between reality and expectations).
Incongruity	Self-identity and subjective values are grossly incompatible with role expectations.
Overload	Too much is expected in the time available.
Underload	Role expectations are minimal and underuse the role occupant's abilities.
Overqualification	Occupant's motivation, skills, and knowledge far exceed those required.
Underqualification	Incompetence; the role occupant lacks one or more of the necessary resources (commitment, skill, knowledge).

Source: Adapted from Lipson, J. G., & Dibble, S. L. (2005). *Culture and clinical care.* San Francisco, CA: USCF Nursing Press.

The working mother is an example of role conflict and role overload; she may struggle with her dual professional and maternal roles. A decision to quit work and devote all her time to mothering may contribute to a lack of self-worth or identity. A decision to continue both roles may generate feelings of guilt because the new mother feels she is neglecting her family's needs. Reducing her work hours is a behavioral change she may make to allow more time for her family. She thus receives the positive reinforcement of employment yet has more time for family and her maternal role. If she does not modify her roles, she may experience further stress and anxiety. To be effective, role change requires several steps. Such change develops through gradual, continuous, and dynamic processes based on the individual's needs and those of relevant others. The steps to successful role change include identifying the role of the relevant other (or others), identifying the expectations of the new role, developing the abilities for it, taking on the new role, and modifying it.

PARENTAL ROLE

Certain behaviors define the role of the parent. It is also important to remember that not all families today are composed of mothers and fathers, so identifying who is taking on the parenting role is important to understand how to best support families. Several factors influence these behaviors: cultural background, personality, previous parenting and life experiences, degree of attachment to the infant, and expectations that parents have of themselves and the infant or child. A child changes everything in the

close-knit relationship of the parents (Tryphopoulos, Letourneau, & Ditommaso, 2014). They must take on a new role; they are not just partners sharing a relationship, they are now mothers and/or fathers as well. Feelings of inadequacy, conflict, and fatigue are often apparent during the transition and may adversely affect both existing relationships and those just developing between parent and child (Brett, Staniszewska, Newburn, Jones, & Taylor, 2011). Parenting remains the only major role for which there is little systematic preparation in our society. Difficulties encountered in the early stages of parenting may adversely affect all relationships but most especially the relationship between partners (Jackson, Newsome, & Beaver, 2016). These difficulties can arise even if the new child is not the first child in the family unit; each additional member of the family brings unique joys and challenges.

The situation in which a person must parent also influences behaviors. Parents faced with a crisis must modify their roles and adapt to the necessary changes encountered with the crisis. Role and behavior changes can cause considerable stress, especially if these changes occur abruptly (Treyvaud et al., 2011). Maternal depression is a well-known phenomenon encountered by many mothers both during pregnancy and in the postpartum period. Mothers who must encounter the NICU are at particularly high risk for developing depression (Barnard et al., 2011; Beck, 2011; Rogers, Kidokoro, Wallendorf, & Inder, 2013). Parents suffering from mental or physical illness or those who are chemically dependent can have limited coping abilities and social support (Gray, Edwards, O'Callaghan, & Cuskelly, 2012). Screening at admission, and throughout the infant's stay in the NICU, is important so that support and treatment can be provided for at-risk mothers (Rogers et al., 2013). Other interventions might include enhancing the mother's ability to become more engaged in her infant's care, as well as helping her connect with other mothers in similar situations and finding resources for them in the community (Gray et al., 2012; Zelkowitz et al., 2011).

Single, adolescent, or first-time parents are also at a disadvantage. They may lack maturity and coping skills because of limited life experiences and unavailable or inappropriate social support systems. These disadvantaged situations may inhibit the development of the parent–infant relationship and thus impair parenting behaviors regardless of whether the infants are high-risk, preterm, or full term (Gray et al., 2012). In addition, people parent differently and take on roles differently (Boykova & Kenner, 2010). These differences are not wrong or right; they are just differences that need to be acknowledged and accepted. Parents who have experienced some type of loss through infertility may also have more difficulties parenting their infant in the NICU since their personal investment in having a child may be causing role strain accompanied by increased stress and anxiety (McGrath, Samra, Zukowsky, & Baker, 2010). Sensitivity to these experiences and previous losses is important in understanding how best to support these parents in the NICU. Lastly, in the NICU women are often the focus and men can be easily overlooked and not well understood or supported (Boykova & Kenner, 2010; Cleveland, 2008). Care of men in this high-risk situation is changing but it still is an area where we need to improve and provide optimal care and support (Kim, 2018).

Infant-related factors can also interfere with parental attachment and subsequent parenting behaviors. An example is an infant born with a congenital anomaly (Neel, Stark, & Maitre, 2018). Many of these infants may be mentally or physically disabled for a lifetime, which interferes with the parents' expectations of their infant (Brooks et al., 2012; Flacking et al., 2016; Watson, 2010). A visible anomaly is particularly difficult for parents because society places such emphasis on appearance. An infant with an easily correctable anomaly is tentatively unacceptable to society, until the anomaly has been corrected. A visible, noncorrectable anomaly has a greater impact on the parents and other family members. This stigma may include preterm infants who have deficits related to their untimely birth, such as blindness, deafness, or severe respiratory compromise. These parents may suffer from chronic sorrow and the child may grow up hindered by the expression of the "vulnerable child syndrome" (Samra & McGrath, 2009; Coughlin & Sethares, 2017). It may be helpful to connect these families with support groups or other families with children with similar disabilities or diagnoses (Al Maghaireh, Abdullah, Chan, Piaw, & Al Kawafha, 2016; Liu, Chao, Haung, Wei, & Chien, 2010; Stefana & Lavelli, 2017).

A life-threatening or terminal illness in a child is another situation that may interfere with parenting attachment and behaviors (Pelentsov, Fiedler, & Esterman, 2016). Parents may hold back their feelings for the child to try to protect themselves from loss and pain if the child dies (Currie et al., 2016). This inability to attach to their infant interferes with the parenting experience and may affect the child's development if the child lives past the previously expected life span.

At any birth or other interaction between a parent and his or her child, the nurse must identify adaptive and maladaptive parenting behaviors. Adaptive behaviors indicate that both the infant's and parent's needs are met and the parent–child relationship can be established. Parents have different ways of expressing their parental roles based on gender differences alone (Boykova & Kenner, 2010; Mundy, 2010). Table 35.2 identifies parenting behaviors the nurse can use as a foundation for assessing adaptive or maladaptive behaviors. It is important to remember that these are guidelines and must be adapted individually to each parent based on his or her personality and the specific situation.

PARENTING DURING CRISIS

Taking on the parenting role is a major life task for a couple. The crisis of having a critically ill newborn in the NICU compounds the stress of that task. Whether the family unit attains growth from a positive resolution of this crisis or splinters because of a maladaptive adjustment largely depends on the partnership formed with caregiving and the quality of support provided (Aronson, Yau, Helfaer, & Morrison, 2009; Beck, 2011). The memory of what happens in the first days after a traumatic birth often stays with a family forever. Just ask a mother to describe her birth experience, and she will talk for hours, explaining every detail (Beck, 2011). Consequently, the relationships formed and interventions provided during the initial trauma can be critical to the adjustment and continued growth of the family unit (Barnard et al., 2011; Cleveland, 2008).

Parent Responses

Crisis can be defined as an upset of a steady state; that is, a period of disequilibrium precipitated by an inescapable demand to which the person is temporarily unable to respond adequately. The birth of a critically ill infant represents two types of crises for parents. The birth of any infant is a developmental crisis, a natural transitional phase in the lives of parents. When the infant is premature or ill, parents also experience an accidental and unexpected crisis. The meaning of the event for the family and the resources available to deal with the event are variables that determine the scope of the crisis. With the technological advances in medicine, some families are now able to better prepare for and make decisions about their child's prognosis and medical needs before birth. For example, many infants with gastroschisis or other anomalies are diagnosed during a prenatal ultrasound examination. In such cases, families have the opportunity to better plan for the birth and to make decisions with the healthcare team in a more conducive

TABLE 35.2

GUIDELINES FOR ASSESSING ADAPTIVE AND MALADAPTIVE PARENTING BEHAVIORS

Adaptive Behavior	Maladaptive Behavior
Delivery	
Attempts to position head to see infant as soon as delivered and while infant is on warming table	Does not position head to see baby
When shown infant: • Smiles • Keeps eyes on infant, looking at all parts exposed • Attempts a face-to-face position • Uses fingertip touch on face and extremities • Asks to hold baby • Partly opens blanket to see more of infant • Talks to baby • Asks questions about baby	When shown infant: • Frowns • Stares at ceiling • May not look at infant • Stares at baby without expression • Does not assume *en face* position • Does not touch baby • Does not ask to hold baby • Declines offer to hold baby • If infant is placed in her arms, lies still, and does not touch or stroke baby's face or extremities • Does not talk to baby • Asks few or no questions
Makes positive statements about baby: "She's so cute!" "He's so soft!"	Makes no comments or makes only negative statements: "She looks awful." "He's ugly."
May cry out of joy or relief that infant is normal or of desired sex	May cry, appearing unhappy or depressed
May smile and cry at the same time (to differentiate from crying out of disappointment, note facial expressions and verbal statements)	When asked why she is crying, states she is disappointed in baby
Expresses satisfaction with or acceptance of infant's gender: "We really wanted a girl, but it's more important that he's healthy." "I can't believe it's a boy, at last!"	Expresses dissatisfaction with baby's gender: "Not another girl. I should have known better than to try again for a boy." "I don't even want to see him." May use profanity when told gender
Predominant affect: appears pleased and happy	Predominant affect: appears sad, angry, or expressionless
Suddenly decides she wants to breastfeed	Suddenly decides against breastfeeding
First Week	
Initially uses fingertips on head and extremities; progresses to using fingers and palm on infant's trunk; eventually draws infant toward her, holding infant against her body	Uses fingertip touch without progressing to palm on trunk or drawing infant toward her body
Snuggles infant to neck and face	Does not hold infant to neck or face
Makes spontaneous movements, kissing, stroking, and rocking	Makes few or no spontaneous movements with infant
Talks to infant with positive manner and tone, uses appropriate language, speech, and content	Uses curt language or content
Attempts to establish eye contact by moving infant, assuming *en face* position, or shielding infant's eyes from light	Does not use *en face* position or attempt to establish eye-to-eye contact
Handles and holds baby at times other than when giving direct care	Handles baby only as necessary to feed or change diapers

(*continued*)

TABLE 35.2

GUIDELINES FOR ASSESSING ADAPTIVE AND MALADAPTIVE PARENTING BEHAVIORS (*continued*)

Adaptive Behavior	Maladaptive Behavior
Relaxed with child; relaxed posture, muscle tone	Rigid posture, tension, fidgeting, seems somewhat agitated
Smiles at baby frequently; changes affect appropriately, such as when infant cries	Rarely smiles at baby or smiles all the time without change in affect
Makes many specific observations of infant: "Her eyes look like they might turn brown." "One foot turns in just a bit."	Makes no observations or makes few observations that are either general or negative
Discusses infant's characteristics, attempting to relate them to others in the family: "He has my ears but his daddy's chin." "She really doesn't look like either of us, she just looks like herself."	Does not discuss infant's characteristics in relation to characteristics of family members
With a positive manner, uses animal characteristics to describe baby: "She's just like a cuddly little kitten." "His hair feels like down."	In a negative or hostile manner, uses animal characteristics to describe: "She looks awful, just like a drowned rat." "He looks like an ape to me."
Asks questions about caring for infant discharge	Asks no questions about care
Seeks information about the child; asks appropriate questions	Does not ask questions or questions are not appropriate
First Few Weeks **(if infant remains hospitalized after mother has been discharged)**	
Calls every day or every other day	Calls less frequently than every other day or not at all
Is present at bedside a minimum of twice a week	Is unable to be present at least twice a week, or is not present at all
Stays at bedside for a minimum of 30 minutes	Stays at bedside for <30 minutes
Asks specific questions about infant's condition	Asks no specific questions
Asks appropriate questions frequently	Asks inappropriate questions
Spends most of the time at bedside participation in care while looking at and handling infant	Spends most of the time at bedside observing unit activities and other infants (this may be normal behavior for the first few times the parent is in the NICU); has little or no interaction with infant even though she/he does participate in caregiving with encouragement
Becomes involved with care when encouraged and supported by staff	When encouraged by staff to participate in care, refuses, or decides to leave the NICU, or performs only minimal care
Although the parent is not able to be at the bedside often, when is able to be present the time at the bedside lasts longer than 30 minutes, makes statements about missing infant (e.g., says that she misses infant at home or that she/he wishes she/he could be present more often and stay longer)	Makes no statements about missing infant, or states that she/he misses infant at home and wishes she could be present more often, but comments are not validated by frequent or lengthy time spent at bedside with infant
Expresses reluctance to terminate time at the bedside; is reluctant to leave	Leaves nursery with little hesitation
Waits until infant is asleep before leaving; touches or talks to baby just before leaving; may stand outside window and look at baby before leaving unit	Frequently asks nurse to complete feeding or to change and settle infant
Expresses a desire to participate in holding the infant	Seems afraid to hold infant or participate in care
Expresses a desire to participate in skin-to-skin holding	Finds it difficult to participate in skin-to-skin holding

(*continued*)

TABLE 35.2

GUIDELINES FOR ASSESSING ADAPTIVE AND MALADAPTIVE PARENTING BEHAVIORS (*continued*)

Adaptive Behavior	Maladaptive Behavior
Expresses desire to protect the child, aware of environmental hazards, actively protects	Protective behaviors not exhibited
Is available and willing to learn new things to better care for the child	Is unwilling to learn caregiving skills
Supportive of partner in caring for the child and participating in caregiving, holding, etc.	Communication between partners is distant or nonexistent
First Months	
Holds infant close to her/his body	Does not hold infant securely against body
Supports infant's trunk and head in position of comfort	Head and body of infant are not well supported
Muscles in her/his arms and hands are relaxed and conform to curvature of infant's body	Shoulder, arm, and hand muscles appear tense; hands and fingers do not conform to infant's body
During feedings, holds infant in well-supported position against her body	Holds infant away from her body during feedings or props infant or bottle
Positions during feeding so eye-to-eye contact can occur	Position during feeding prevents eye-to-eye contact
Minimizes talking to infant while baby is sucking	Continues talking to infant during feeding even though infant is distracted and stops sucking
Refers to infant using given or affectionate name	Refers to infant in impersonal way (e.g., "the baby," "she," or "it")
Plays with infant at times unrelated to direct care	Handles infant mainly during caretaking activities
When infant is in infant seat, playpen, or crib, frequently interacts with baby	Leaves infant for long periods in infant seat, playpen, or crib, interacting only after infant becomes fussy
Places infant, when awake, in an area where baby can observe and interact with others	Leaves infant, when awake, alone for long periods in bedroom or isolated area
Occasionally leaves infant with someone else	Frequently leaves baby with someone else or refuses to leave baby with someone else
Uses discretion in selecting babysitter and provides instructions on baby's routines, likes, and dislikes	Does not use good judgment in selecting babysitter; provides inadequate or no instructions for care
Provides infant with routine well-baby care; carries out medical plan for management of specific problems or conditions (e.g., thrush, anemia, or ear infection); makes additional phone calls or additional visits to physician	Fails to provide infant with well-baby care, seeking medical assistance only after problems, or keeps all appointments and makes emergency room visits for imagined or insignificant problems
Remains close to infant during physical examinations and attempts to soothe baby if infant becomes distressed	Remains seated at a distance from the examination table; does not soothe infant during examination; frequently arranges for someone else to take infant for medical appointments
Makes positive statements about parenting role	Makes negative statements about parenting role

Source: Modified from Hall-Johnson, S. (1986). *Nursing assessment and strategies for the family at risk* (2nd ed.). Philadelphia, PA: Lippincott William & Wilkins.

and supportive environment. The ability to anticipate the needs of the child reduces the sense of crisis for these families with the birth of the child.

Families of a premature or sick newborn react in different and individual ways. Some common responses are anxiety, guilt, fear, resentment, and anger. During the illness of a newborn, the parents must face many issues; two important ones are the loss of the perfect child they have anticipated and a fear that their infant may die (Beck, 2011; Cleveland, 2008). In general, excitement and a flurry of preparation surround the birth of a child. Family celebrations help parents share the anticipation of a new infant with friends and extended family members. Parents spend much time imagining what this child will look like and dreaming about the joys of parenting. The parents experience disappointment when the infant or pregnancy is not as anticipated. They may feel a sense of isolation from other parents who have a normal pregnancy or infant. They may even have feelings of isolation from each other or from close family members. The inability to produce a healthy infant or to protect the infant from the invasive and painful environment necessary to sustain the child's life may cause feelings of inadequacy. For some parents, the role they believed they would assume seems impossible to attain in the environment of the NICU, where often it seems everyone else is making decisions about the fate of their infant (Cleveland, 2008; McGrath, 2007b). Parents seldom have had experience with the NICU before and the intensity of the situation is heightened even more by the fact that they and their infant are center stage.

To move forward with the attachment process, parents must reconcile their idealized image of the child with the actual infant. They mourn the loss of the perfect child that was expected and encounter anticipatory grief for the infant whose life may now be in jeopardy (Caeymaex et al., 2012; Currie et al., 2016; Shah, Clements, & Poehlmann, 2011). The birth of an ill or a premature infant often places parents in a state of disequilibrium; nothing is as it was before. For many parents, hope is an important emotional concept during this time of crisis (Ingram et al., 2017). Hope provides some equilibrium that things will get better for their infant and for themselves. However, hope can also lead parents to develop high expectations for their child that may be in conflict with the expectations of the healthcare team (Nordheim, Rustøen, Solevåg, Småstuen, & Nakstad, 2018). These different expectations can lead to more conflict and role strain as families are trying to maneuver the difficult situation of the NICU and understand how to assume their parenting role and best support their child (Roscigno et al., 2012).

Mothers of premature infants have had the emotional work of pregnancy cut short and thus are often psychologically unprepared for the birth (Beck, 2011; Caeymaex et al., 2012). If the mother had felt ambivalent about the pregnancy, she may believe that the infant's illness is somehow punishment for those emotions. A mother may also feel guilty that she could not carry the infant to term, even if no reason can be found for the baby's premature birth.

Many parents of sick newborns go through identifiable stages of grief and loss with very emotional reactions (Currie et al., 2016). The initial response usually is one of overwhelming shock, characterized by irrational behavior, crying, and feelings of helplessness and despair. Families at this stage have difficulty with organization because their lives have been disrupted by the unexpected birth. They may feel as if everything is in chaos and the situation is out of their control. Substance abuse, adolescent pregnancy, clinical depression, and domestic violence can increase the chaos and vulnerability of these families (Cleveland, 2008). Parents also may feel guilt over the premature delivery or the infant's illness. Self-blame often characterizes these feelings ("If only I had stayed home the day I noticed the spotting"). Parents may try to escape the situation by using denial ("Everything will be fine in just a few days"). At the bedside in these initial days, parents may focus on facts they can understand and avoid issues they do not. To healthcare providers, this may seem as if the parents aren't listening or that they are unwilling to hear the information provided, yet the parents are trying to cope with what to them is an overwhelming situation (Hardy & McGrath, 2008; McGrath, 2007b).

Intense feelings of resentment and anger follow denial. Parents may direct these feelings at themselves, the infant, members of the healthcare team, God, or even each other as parents. They may also experience feelings of ambiguity and may fear the infant's physical and mental outcome. For these reasons, they may avoid emotional involvement with the infant to protect themselves from the pain of possible loss. A lessening of the intense emotional reactions and an increased ability to begin caring for their infant's emotional and physical needs are characteristic of adaptation and of taking on the parenting role. Reorganization is the final stage; at this point, parents come to terms with their infant's problems. This can take from a few days to several months. In some cases, these feelings of loss and grief may never be resolved (Caeymaex et al., 2012; Currie et al., 2016). Throughout these stages, often it is hope that helps parents to move forward and believe that a new day will bring better outcomes for their child (Nordheim, Rustøen, et al., 2018).

Factors That Affect Parenting Skills

Certain factors affect a person's ability to acquire parenting skills during the NICU experience (Box 35.3). Parents are unable to attach and detach at the same time; these two tasks are incongruent. Parents need time to detach or grieve for the lost perfect child before they can begin to attach to the ill infant. This adjustment may take days or even weeks and for some parents attachment may never occur (Shah et al., 2011).

Parents in the NICU environment face physical, mechanical, psychological, and emotional obstacles during this difficult time. In this chapter, we refer mostly to the psychosocial behaviors of parenting and becoming a family, but it is important to note that these behaviors also have implications for the parent's health and personal well-being (Howland, Pickler, McCain, Glaser, & Lewis, 2011). These physiological issues cannot be ignored since parents who do not attend to their personal and physical needs are not as able to attend to the needs of their child (Turner, Winefield, & Chur-Hansen, 2013). Evidence supports that an infant's appearance and experience of painful procedures, as well as the perceived

Box 35.3

FACTORS THAT INFLUENCE FAMILY REACTIONS TO A CHILD'S HOSPITALIZATION OR ILLNESS

- Severity of the illness and the threat to the child
- Previous experience with illness or hospitalization (or both)
- Familiarity with the medical procedures involved in diagnosis and treatment
- Available support systems
- Available coping strategies of family members
- Number and degree of other family stresses
- Cultural or religious beliefs
- Communication patterns of family members

severity of the child's illness, all contribute to the degree of stress experienced by parents (Heidari, Hasanpour, Fooladi, & Awat, 2015). A nurse who can properly identify the specific stressors with each parent or family has the opportunity to assist them in reducing those stressors and promoting adaptation for the family unit (Beck, 2011; Craig et al., 2015).

The nurse is potentially the principal barrier to parenting in the NICU because the nurse can be seen as the gatekeeper of the infant (Latour, Hazelzet, Duivenvoorden, & van Goudoever, 2010). In reality, the infant belongs to the family and not to the medical team. For parents to attach to their infant, a welcoming, calming environment in which they feel comfortable is essential in the NICU (Venkataraman, Kamaluddeen, Amin, & Lodha 2018; Box 35.4). This kind of environment encourages parents to grow in their primary caregiver role so they can develop skills needed to be advocates for their child. This advocacy is essential for the infant's continuing development, especially if the child has special needs (Franck & Axelin, 2013). Meiers, Tomlinson, and Peden-McAlpine (2007) developed the Family Nurse Caring Belief Scale to examine nurses' beliefs about FCC activities. This instrument can be used to understand how nursing staff perceive their own delivery of FCC and as a means to examine changes in FCC in a particular NICU environment over time.

Parents react to stress and grief in different ways (Cleveland, 2008). A man may isolate himself and become engrossed in his work and may not share his feelings with a woman. A man often tries to be strong for the woman and may become protective, sometimes choosing to shield her from painful information (Hardy & McGrath, 2008). A wife may view her husband's stoic behavior as cold and unfeeling. Both may have difficulty discussing the child because of their own grief or guilt feelings. Normal postpartum blues can increase the mother's sensitivity to this situation and lead to further depression (Beck, 2011). She may cry for no real reason and feel embarrassed about irrational behavior. Existing weaknesses in their relationship are often magnified. Parents are often separated in their feelings at this time and fears may arise that their relationship is falling apart at a time when they each need the other. Lack of communication can lead to isolation and feelings of resentment in each of the partners. Each may make assumptions about the other's feelings, resulting in misconceptions. The need to communicate and share in each other's experiences is especially true if the child has special needs or a developmental disability. These misconceptions, along with gender differences in coping, may continue for a lifetime if they are not recognized and shared during the neonatal period (Poehlmann, Miller Schwichtenberg, Bolt, Dilworth-Bart, 2009). Helping parents understand that their feelings are not unusual is important to facilitate the sharing of these feelings with their partner. Some people may require counseling during this time.

Other stressors in the family, such as the needs of other children, financial concerns, illness of family members, or marital stress, can complicate the situation (Curtis, Foster, Mitchell, & Van, 2016). For example, factors that can influence the degree of stress perceived by the family include the availability of appropriate emotional and psychological support among family members and from friends and the availability and use of community resources (Curtis et al., 2016; Wang, He, & Fei, 2016). Maintaining a support system and using community resources and professional assistance are excellent coping strategies for dealing with the crisis. Coping abilities demonstrated during previous crises often can predict how parents will cope with the current crisis. In an acute crisis, the family may be unable to use the resources available adequately because of lowered self-esteem, reduced family cohesiveness, and impaired family communication. Interventions during this time should focus on helping parents recognize and use available coping strategies. Communication patterns could be impaired because of anger or emotion derived from the crisis situation (Curtis et al., 2016). Therefore, at times the family may require outside assistance; they may be unable to use or maintain the community resources required without this support (IPFCC, 2017).

A stressful situation has a specific meaning for each family and for each member of the family because of previous experiences and the family's perceptions of these demands and their personal capabilities. For example, a sepsis workup may not seem particularly stressful to the healthcare team but may be very stressful to parents and families (Newnam & McGrath, 2010). For some families, the least hint that their infant is sicker or more unstable can be devastating. Certain personality types thrive on stress and deal effectively with any crisis. Others are unable to deal with even the smallest crisis. For example, if a family acknowledges a stressor as a "challenge" or can bestow meaning on the situation, such as believing that "it is the Lord's will," adaptation will likely be more successful. Maladaptation results if the family interprets the stressor as threatening or undesirable. The family's expectations for themselves and this new child affect parenting skills (Giambra, Broome, Sabourin, Buelow, & Stiffler, 2017). Each partner draws on his or her own childhood experience for parenting role models. The meaning the stressor has to the family also depends on the family's identity, cultural beliefs, and worldview. The family's identity comprises the values of the family which are seen in the routines and rituals that develop in individual families. Stressors may disrupt these routines and rituals, threatening the development, maturation, and stability of the family system (Craig et al., 2015; IPFCC, 2017). The family's worldview is based on how the family interprets reality, its core belief system (religious and cultural beliefs), and its purpose in life. The way a family handles its problems or deals with change often is based on the family identity and worldview. The family worldview is the most stable of the three levels of meaning but even this can be shattered by a severe crisis (Craig et al., 2015).

The coping strategies are cognitive and behavioral components of the effort to handle the stressful event, that is, what

Box 35.4

CREATING A WELCOMING ENVIRONMENT IN THE HOSPITAL FOR FAMILIES

1. When the opportunity presents before the birth, prepare the family for the infant's admission to the NICU and hospital course.
2. Give a special orientation for families who have undergone an emergency admission.
3. Provide for the needs of families who have traveled long distances.
4. Make fathers as welcome as mothers.
5. Meet the needs of siblings and other family members.
6. Enable families to be together as much as possible; have open visiting hours 24 hours a day.
7. Encourage families to bring items from home to create a personalized environment that makes their child feel more at home.
8. Provide privacy for family when present at bedside.
9. Encourage family participation in the child's care.
10. Help the family stay in touch with extended family members and support-givers in the community.

Source: Adapted from Institute for Patient- and Family-Centered Care. (2017). *Advancing the practice of patient- and family-centered care in hospitals: How to get started*. Bethesda, MD: Author. Retrieved from http://www.ipfcc.org/resources/getting_started.pdf

the family "does" to handle the stress. These strategies can be emotion-focused (i.e., strategies for controlling the emotions the crisis has engendered, such as denial or anger) or problem-focused (i.e., action-oriented strategies to manage the crisis). Coping behaviors are learned, and families can use any or all of the major coping functions in a crisis situation. Emotion-focused strategies are used most often in the adjustment phase of a crisis and problem-focused strategies are used more in the adaptation phase (Foster et al., 2018).

CULTURAL PERSPECTIVES

Definitions

Some key definitions are important to an understanding of cultural perspectives.

- Ethnicity: a common ancestry through which individuals have evolved shared values and customs
- Culture: socially inherited characteristics, such as rituals, thoughts, beliefs, behavior patterns, and traits inherent within a certain racial, religious, or social group
- Acculturation: changing one's cultural patterns and assimilating behaviors consistent with those of the society in which one lives; this task can be done by learning the language, intermingling socially, or developing friendships, or through marriage or relationships formed in school or workplaces
- Religion: a belief in divine powers; a system of beliefs, practices, and rituals

The family has always been seen as the critical social unit for passing on beliefs and values in our society. Healthcare professionals must recognize and be sensitive to the influence of culture and ethnicity on a child's development and the family's response to illness or a chronic condition (Lipson & Dibble, 2005). The family's cultural ties provide support and a sense of stability during times of upheaval and stress.

The meaning of family varies with the ethnic or cultural background of the family (Lipson & Dibble, 2005). Differences exist across cultures and although there are similarities, it is important not to generalize across social groups. The examples provided here are just that, examples. It is important to work with each family as individuals who may or may not exhibit these characteristics. The concept of immediate family among Anglo-Americans often means the nuclear family of mother, father, and children, although this is changing as other definitions of family are becoming increasingly acceptable in our society. Lesbian, gay, and same-sex partners are now more common and they may be raising children who may need care in the NICU. Parents who are unmarried but living together are also becoming increasingly commonplace in our society.

For African American families, the definition of family often includes extended family members within the community. For Italians, family can often include a very strongly knit group of family and friends extending over three or four generations. The Chinese family can often be defined as all their ancestors and all their descendants. Mexican American families often include close-knit members that include supportive communities that are multigenerational. Differences in family hierarchy can both positively and negatively influence young parents (Al Maghaireh et al., 2016). Understanding and appreciating the uniqueness and differences in the meaning of family across cultures and ethnic groups can assist the healthcare professional in promoting the family's health and supporting the family in times of illness or debilitating conditions (Ardal, Sulman, & Fuller-Thomson, 2011). No judgments should be made and the parents of the child should be able to choose who they believe is their family and their support system, particularly in this time of stress.

Ethnic or cultural groups also differ in the meaning they give to illness and disability, and in when they seek healthcare (Lipson & Dibble, 2005). Although the nurse must recognize that each family and situation must be assessed individually, there are some general characteristics that may be helpful in understanding differences seen among ethnicities. For example, generally members of an Italian family rely on the family for help when ill and seek medical help only as a last resort. They use words and emotions to convey the meaning of an experience to others. The close-knit family is of vital importance, and the nurse must respect the family as a cohesive unit. In general, African Americans often have an underlying distrust of the healthcare system. To effectively work with African American families, the nurse must be supportive of the family or empower the family to solve their own problems, providing as much information as possible. Racism and oppression have left their marks on these families and healthcare providers must facilitate the family to be advocates for the ill child, to cope constructively with problems, and to deal with an unknown future if disabilities persist (Al Maghaireh et al., 2016). Members of some ethnic groups (e.g., Irish, African Americans, and Norwegians) consider illness to be the result of an individual's own sins, actions, or inadequacies. Native American Indians often consider illness or disability the result of misconduct, for which the family is punished (Lipson & Dibble, 2005). The illness is part of the whole person. Native American Hawaiians may view illness as an imbalance in the energy or harmony within the family. The illness is part of wellness and this disharmony is a normal part of life. Anglo-Americans may view illness as stemming from a scientific cause that is outside the family. The illness is foreign and intrusive to the individual and the family. Considering these traditional characteristics may be helpful in understanding the context of culture.

When a child is hospitalized, several important issues must be discussed with the family:

- What support the family wants
- Preferences regarding language, food, holidays, religion, and kinship
- Beliefs with regard to health, illness, and technological advances
- Health practices (e.g., immunizations, annual physical examinations)
- Habits, customs, and rituals which could affect health

An understanding of cultural differences can help the nurse provide care, determine the meaning of the illness or disability to the family, and assist the family in interventions appropriate to their culture (Brooks et al., 2012). This understanding also shapes parent and staff expectations of each other and of the ways in which care is provided. Taking the time to ask questions and understand the cultural influences on families cared for in the NICU can facilitate communication between families and healthcare providers (Ichijima, Kirk, & Hornblow, 2011). Language can often be a barrier to providing care and understanding the needs of families. Providing appropriately supportive interpreters to families in the NICU is extremely important to supporting families and helping them to understand the needs of their infant (Matsuda & McGrath, 2011).

PROMOTING PARENTING IN THE NICU

A major nursing goal in the NICU for care of the family is to optimize parenting skills and discharge an intact family unit (Boykova & Kenner, 2012; McGrath, 2012). There are different ways to ease parental anxiety during the NICU experience. Open visiting policies encouraging unrestricted parent presence throughout the

24-hour period provides parents more opportunities to be with their infant while allowing them to manage other responsibilities outside the NICU (Raiskila et al., 2017). Unrestricted access to the infant allows the attachment and parenting processes to be fostered (Baker & McGrath, 2011).

Facilitating the Attachment Process

The attachment process for most parents begins at birth, or perhaps before birth during the pregnancy process. With a sick or premature infant, this process can be delayed until the parents can establish eye contact with and begin touching and caring for their infant. Bonding and attachment are enhanced by supporting parents to touch and hold their infant as soon as the child's condition allows, especially SSC (D'Agata, Young, Cong, Grasso, & McGrath, 2016; Casio et al., 2018; Neu & Robinson, 2010). The preterm neonate's physical appearance, disorganized behavioral responses, and variable physiological response to touch can cause much anxiety in the parents as they attempt to interact with their infant. However, it is important that the bedside nurse, well versed in what the sick or premature infant will tolerate, explains those maturational limitations to the parents. It is vital that parents understand an infant's immaturity and inability to navigate often overwhelming sensory experiences; otherwise, parents may misinterpret the infant's behavioral cues or detach from their infant in an effort not to bother or overstimulate the infant. Interventions that focus on helping parents to understand and respond sensitively to infant cues have been found to facilitate both the infant and the family (Moradi, Arshdi-Bostanabad, Seyedrasooli, Tapak, & Valizadeh, 2018; Mortessen & Mastergeorge, 2014; Zelkowitz et al., 2011). It also is important for the nurse to work with the parents to help them recognize an infant's distress signals (e.g., hiccups, apnea, cyanosis, bradycardia, or mottling) so that parents can gauge their caregiving interactions by their infant's unique cues and behavior (Als & Gilkerson, 1997; Raines & Brustad, 2012; Zelkowitz et al., 2011).

Parent participation in caregiving must begin at admission (Raines & Brustad, 2012). Soothing touch, providing containment, gentle infant massage, holding the infant, bathing, and SSC, or "kangaroo care," are just a few of the "high-touch" avenues for promoting parenting in the NICU (Casio et al., 2018; Neu & Robinson, 2010). Each of these supportive strategies should be provided to all infants in the NICU and reserved for families to implement with their infant. When parents are providing these interventions, there are physiological and behavioral benefits for the infant as well as benefits to parents, including early bonding, increased confidence in parenting skills, and a sense of control (Nordheim, Anderzen-Carlsson, & Nakstad, 2018; Vance & Brandon, 2017). Parents who have the opportunity to participate in caregiving and get to know their infant begin to have a sense of confidence that their infant is well cared for and may survive (Amin et al., 2018; Pichler-Stachl et al., 2011; Reid, 2007). Nurses can use several key techniques to prepare parents for working with their infant and the technology in the NICU:

- Build on parents' strengths
- Provide encouragement and use constructive criticism only as necessary
- Encourage parents to discuss their concerns and emotions
- Provide parents with information specific to their infant's care or condition
- Clarify information that parents have received through other channels
- Draw the parents' attention to positive points about their infant, including how the child responds to the parents
- Keep the channels of communication open by remaining nonjudgmental

Interventions with families must acknowledge the individuality of each member and of the family as a unit. Understanding that the needs of the whole are not equal to, greater than, or less than those of the parts is often a difficult concept for the neonatal nurse, who sometimes sees his or her role as involved more specifically with the care of the high-risk infant. Researchers repeatedly have found that hospital-based neonatal nurses view caring for families as not within their realm of practice (and certainly not a priority in their practice), but as something extra they do "when there is time" (Meiers et al., 2007; Mosqueda et al., 2013). These views are not congruent with developmentally supportive FCC practices. Optimal care requires that healthcare providers adopt a family-centered philosophy (Cisneros Moore, Coker, DuBuisson, Swett, & Edwards 2003; Latour et al., 2010). Full implementation of a family-centered approach depends upon the support of the unit leadership and the institution (Milette et al., 2017a, 2017b). One way to facilitate greater involvement of families is to form parent advisory boards that guide implementation of practices in the NICU (IPFCC, 2018). Staffing plans that allow healthcare providers, especially nurses, time in their schedules to work collaboratively with families must be a priority if developmentally supportive family-centered practices are truly fundamental to the philosophy of care in the NICU (IPFCC, 2017).

Parents have repeatedly reported that they felt that healthcare professionals did not recognize them as the expert caregivers of their child and the constant in their child's life (DeMauro, Cairnie, D'Ilario, Kirpalani, & Schmidt, 2014; Zhang, Kurtz, Lee, & Lui, 2014). This perception may lead to mistrust in the developing partnership between the caregivers and the professionals and may intensify the stress for the parent and, ultimately, the child during the hospitalization (Aagaard, Lall, Ludvigsen, Uhrenfeldt, & Fegran, 2018). Acknowledging that parents are the experts and nurses are the consultants to whom parents come to for information or support is a shift that remains difficult for some professionals (IPFCC, 2017). Parents are empowered by nurses when they are respected, involved in the plan of care, provided with complete, unbiased information, and given a sense of control in the healthcare setting (IPFCC, 2017; Pichler-Stachl et al., 2011). To support full integration and implementation, see Table 35.3 for evidence-based strategies and interventions that empower and support families during newborn intensive care.

Caretaking is a normal part of parenting. However, parents of sick or premature infants are often deprived of the time to prepare psychologically for caring for a high-risk infant and to develop the caretaking skills to feel confident (Amin et al., 2018; Raines & Brustad, 2012). If nurses do not allow the family to become regularly involved in caretaking tasks, parents may feel inadequate or may resent the nurses. Positive reinforcement builds self-confidence in parenting abilities. Interventions that empower families are important to both short- and long-term outcomes for the infant and the family (Mortessen & Mastergeorge, 2014).

Providing Information

Throughout the infant's illness, parents need accurate, timely information about their child's condition (Box 35.5). If the information provided is not timely and does not anticipate the needs of the parents as related to their relationship with their infant, it may not be helpful and may actually hamper the care (Herd et al., 2014). Information should be direct and honest and should not be contradictory, so limiting the number of professionals providing information is often helpful. Parents also appreciate the use of drawings and diagrams when their infant's condition is explained to them, and they appreciate being encouraged by staff members to ask questions. Presenting this information with some optimism

TABLE 35.3

EVIDENCE-BASED FAMILY-CENTERED CARE STRATEGIES TO SUPPORT INFANTS AND FAMILIES IN THE NICU

Intervention	Level of Evidence	References
Encourage the family to spend as much time with their infant as possible; support nonseparation	V	• Boundy et al. (2016)
	V	• D'Agata et al. (2017)
	III	• Feeley et al. (2016)
	IV	• Green et al. (2015)
Facilitate and maintain a true collaborative partnership with families	IV	• Aronson et al. (2009)
	V	• Craig et al. (2015)
	IV	• McCormick, Escobar, Zgeng, and Richardson (2008)
	IV	• Meiers et al. (2007)
	VI	• Mundy (2010)
	V	• Reis et al. (2010)
Assist the family in resolving feelings of guilt	IV	• Caeymaex et al. (2012)
	IV	• Shah et al. (2011)
	VI	• Watson (2010)
Facilitate and provide opportunities for families to develop and sustain hope	V	• Bally et al. (2018)
	IV	• Nordheim, Rustøen, Solevåg, Småstuen, and Nakstad (2018)
	IV	• Ingram et al. (2017)
	IV	• Roscigno et al. (2012)
Provide the family with opportunities to learn about infant cues and behaviors to facilitate attachment and decrease a sense of vulnerability	IV	• Samra & McGrath (2009)
	IV	• Makris et al. (2019)
	IV	• Moradi et al. (2018)
	II	• Peyrovi, Mosayebi, Mohammad-Doost, Chehrzad, and Mehran (2015)
	II	• Tooten et al. (2012)
	II	• Zelkowitz et al. (2011)

(*continued*)

TABLE 35.3

EVIDENCE-BASED FAMILY-CENTERED CARE STRATEGIES TO SUPPORT INFANTS AND FAMILIES IN THE NICU (*continued*)

Intervention	Level of Evidence	References
Provide the family with opportunities to hold and touch their child early in the NICU stay	IV	• Casio et al. (2018)
	III	• Campbell-Yeo et al. (2017)
	IV	• Cho et al. (2016)
	II	• Neu and Robinson (2010)
	II	• Ludington-Hoe (2011)
Provide parents the choice to be present during procedures to support their child	IV	• Aronson et al. (2009)
	IV	• Axelin, Lehtonen, Pelander, and Salantera (2010)
	V	• Garfield et al. (2018)
	IV	• Kamphorst et al. (2018)
	IV	• Mangureten et al. (2005)
Facilitate parent presence and caregiving through communication that is welcoming and supportive	V	• Brett et al. (2011)
	III	• Brooks et al. (2012)
	III	• Flacking et al. (2016)
	IV	• Pichler-Stachl et al. (2011)
	III	• Provenzi et al. (2015)
	IV	• Raines and Brustad (2012)
	IV	• Raiskila et al. (2017)
	IV	• Vittner et al. (2018)
Provide parents opportunities to participate in care through scheduling of caregiving to increase their presence	VI	• Baum et al. (2012)
	V	• Cleveland (2008)
	VI	• Gasparini, Hudson, Champagne, Fuchs, and Stephany (2015)
	III	• Kjellsdotter, Lantz, and Ottosson (2018)
Provide support to men and encourage them to participate in care	IV	• Kim (2018)
	VI	• Watson (2010)

(*continued*)

TABLE 35.3

EVIDENCE-BASED FAMILY-CENTERED CARE STRATEGIES TO SUPPORT INFANTS AND FAMILIES IN THE NICU (*continued*)

Intervention	Level of Evidence	References
Screen often and regularly for maternal depression and provide resources to support women (men) as needed	IV	• Bartlett, Nijhuis-van der Sanden, Fallang, Fanning, and Doralp (2011)
	II	• Barnard et al. (2011)
	VI	• Baum et al. (2012)
	VI	• Beck (2011)
	VI	• Brooks et al. (2012)
Provide care that is culturally sensitive	V	• Al Maghaireh et al. (2016)
	IV	• Ichijima et al. (2011)
Introduce the family to support systems in the form of families with children who are undergoing or have undergone similar experiences	VI	• Ardal et al. (2011)
	I	• Al Maghaireh et al. (2016)
	IV	• Domanico, Davis, Coleman, and Davis (2010)
	VII	• Gooding et al. (2011)
	IV	• Macdonell et al. (2013)
	III	• Liu et al. (2010)
	IV	• Treyvaud et al. (2011)
	II	• Stefana and Lavelli (2017)
Provide the family with resources from the community (e.g., spiritual, economic, and social help, as well as information)	V	• Al Maghaireh et al. (2016)
	V	• Bos et al. (2018)
		• Boykova and Kenner (2012)
	IV	• Hägi-Pedersen, Norlyk, Dessau, Stanchev, and Kronborg (2017)
Assist the family in recognizing and using their strengths and coping skills or facilitating development of new coping strategies to decrease stress in the NICU; encourage the family to explore positive ways of coping with the situation	IV	• Aagaard et al. (2018)
	IV	• Amin et al. (2018)
	IV	• Epstein, Miles, Rovnak, and Baernholdt (2013)
	VI	• Howland et al. (2011)
	IV	• Garfield et al. (2018)

(*continued*)

TABLE 35.3

EVIDENCE-BASED FAMILY-CENTERED CARE STRATEGIES TO SUPPORT INFANTS AND FAMILIES IN THE NICU (*continued*)

Intervention	Level of Evidence	References
	IV	• Gray et al. (2012)
	VI	• Nordheim, Rustøen et al. (2018)
	VI	• Watson (2010)
Facilitate positive perceptions of staff by families through staff communication styles	I	• Brett et al. (2011)
	IV	• Breitenstein, Gross, and Christophersen (2014)
	VI	• Dykes et al. (2016)
	IV	• Foster et al. (2018)
	IV	• Franck and Axelin (2013)
	V	• Giambra et al. (2017)
	IV	• Latour et al. (2010)
	III	• McCann et al. (2008)
	IV	• Miyagishima et al. (2017)
Provide education for families that meets their needs and is provided in a supportive style	IV	• Bracht, O'Leary, Lee, and O'Brien (2013)
	IV	• Coulter and Ellins (2007)
	I	• Herd et al. (2014)
	V	• Hill et al. (2018)
	IV	• Morey and Gregory (2012)
	IV	• Neel et al. (2018)
	II	• Shieh et al. (2010)

Rating System for the Hierarchy of Evidence

Level I:	Evidence from a systematic review or meta-analysis of all relevant RCTs, or evidence-based clinical practice guidelines based on systematic reviews of RCTs
Level II:	Evidence obtained from at least one well-designed RCT
Level III:	Evidence obtained from well-designed controlled trials without randomization
Level IV:	Evidence from well-designed case-control and cohort studies
Level V:	Evidence from systematic reviews of descriptive and qualitative studies
Level VI:	Evidence from a single descriptive or qualitative study
Level VII:	Evidence from the opinion of authorities and/or reports of expert committees

RCT, randomized controlled trial.

Source: Adapted from Melnyk, B. M., & Fineout-Overholt, E. (Eds.). (2010). *Evidence-based practice in nursing and health care: A guide to best practice* (2nd ed.). Philadelphia, PA: Lippincott Williams & Wilkins.

Box 35.5

GUIDELINES FOR PROVIDING INFORMATION TO FAMILIES OF ILL INFANTS

Focus the teaching session so as to build confidence and foster independence in the family. Build from strengths of the parents; do not focus on weaknesses.

1. Begin by assessing what the family members already know.
2. Establish a working rapport with the family; work to ease their anxiety and fear and to convey confidence and assurance to family members.
3. Ask family members what they expect to learn from the session and provide information directed toward their concerns.
4. Initially, focus teaching on the diagnosis or current crisis.
5. Use language the family understands; avoid jargon.
6. Include the key characteristics of the plan of care and treatment.
7. Explain the ways in which the illness or medication regimen will affect daily life.
8. Use a variety of teaching materials and styles. All information should first be provided orally and reinforced with handouts to be taken home.
9. Keep the information simple and concrete; reinforce oral communication with handouts. Expect to repeat the information and do so readily.
10. Avoid fear tactics while providing information on both benefits and detrimental effects.
11. Use praise to instill confidence.
12. Include anticipatory guidance.

Sources: Adapted from Baker, B. J., & McGrath, J. M. (2011). Maternal infant synchrony: An integrated review of the literature. *Neonatal, Paediatric, and Child Health Nursing, 14*(3), 2–13; Menghini, K. G. (2005). Designing and evaluating parent educational materials. *Advances in Neonatal Care, 5*(5), 273–283. doi:10.1016/j.adnc.2005.07.003; Morey, J. A., & Gregory, K. (2012). Nurse-led education mitigates maternal stress and enhances knowledge in the NICU. *American Journal of Maternal Child Health, 37*(3), 182–191. doi:10.1097/NMC.0b013e31824b4549

Box 35.6

PROVIDING DIFFICULT INFORMATION

Although difficult information is most often provided by physicians, nurses often are part of the team, especially if the information will be painful to the family. Nurses must know how to support families in these difficult situations. Unexpected news is sometimes considered bad news, yet our approach can change the perspective for the family receiving the news.

1. Whenever possible, difficult information should be delivered with both parents present and/or supportive family members as deemed by the family. Crafting the conversation as sharing "unexpected news" rather than bad news can shape what families hear and understand.
2. Remember the language you use will be how the family shares the news with others, so choose your words carefully. Provide unbiased information that is clear, direct, detailed, and understandable; get to the focus of the discussion quickly.
3. Provide the information with compassion and care in a gentle but confident style; a private, quiet place free of distractions should be used for the discussion.
4. Personalize the information to this baby or child and this family. Use the child's name whenever possible. Begin the conversation by sharing with the family what is going well and congratulating them on their child's successes or strengths.
5. Allow the family time to express feelings and ask questions. Provide support for those feelings and questions. Offer hope about the next phase of the child's journey.
6. Provide information about resources and anticipatory guidance. Speak with the family about what you expect will happen next.
7. Arrange an opportunity for the family to meet another family who has experienced a similar situation or crisis.
8. Follow up with the family after an appropriate time to answer any latent questions or provide further support.

Source: Adapted from Carroll, C., Carroll, C., Goloff, N., & Pitt, M. B. (2018). When bad news isn't necessarily bad: Recognizing provider bias when sharing unexpected news. *Pediatrics, 142*(1), e201–e204. doi:10.1542/peds.2018-0503

allows the family some hope and, as discussed earlier, hope is an important concept for coping with the NICU (Ingram et al., 2017; Nordheim, Rustøen, et al., 2018). Ideally, the information should be presented to both parents at the same time. It should be expressed in simple terms with short explanations. The parents are under much stress and this information may be unfamiliar (Brooks et al., 2012; Menghini, 2005). Facts may need to be repeated several times before they are absorbed. Parents need a clear understanding of the information provided to make informed decisions about their infant's care. Family-friendly language in understandable terms should be used when delivering care and information (Herd et al., 2014; Menghini, 2005). Medical information from a primary caregiver, such as a neonatal nurse practitioner or primary physician, provides consistency, especially when the news is difficult or "bad" (Box 35.6). Consistency in caregiving and information sharing is important so that families are not confused by the different information they receive, adding to their distress and sense of distrust of healthcare providers (Carroll, Carroll, Goloff, & Pitt, 2018; DeMauro et al., 2014; Epstein et al., 2013). Families also need information about when they can be at the bedside, unit policies, equipment, procedures, and treatments their infant is receiving. Direct telephone access allows an update from their nurse or physician at all times. In support of oral communication, written information helps parents remember important facts. In addition, written communication also provides a place to refer to later when the information is more relevant to the care of the infant or when there are more questions (Herd et al., 2014; Menghini, 2005). Information can also be reinforced with digital and online materials (Breitenstein, Gross, & Christophersen, 2014). Providing multiple avenues for information sharing provides better support to families who may not always be ready to take in information when shared but have other ways to obtain the information at a later point in time.

Family Presence During Rounds

In many NICUs the practice of inviting family members to participate in medical rounds is becoming common (Aronson et al., 2009). Families are part of the decision-making process and as such are provided information so that they can, in collaboration

with the medical/nursing team, decide when they would like to be present and make decisions for their child and when they feel they would rather not be involved (Gasparini et al., 2015; McGrath, 2011; Pichler-Stachl et al., 2011). Through their presence in rounds, families are involved in the assessment of and planning for their child (Raines & Brustad, 2012; Reid, 2007; Reis et al., 2010). Caregiving issues related to scheduling of rounds, teaching of medical staff, and confidentiality for families during rounds are still unresolved and remain a concern for care providers (IPFCC, 2013a, 2013b; Morey & Gregory, 2012). However, provision of HIPAA is not a viable excuse for not including families in patient rounds (IPFCC, 2010a, 2010b, 2013a, 2013b). For the most part, units where these practices are now common have found that the partnership between the family and the medical team is worth the effort required to implement such decision-making relationships (Butt, McGrath, & Samra, 2013; Grzyb, Coo, Ruland, & Dow, 2014). Providing for and facilitating the family's role as the constant in the infant's life is the best approach for the infant's long-term development. Critical pathways (see Supporting Families With Caregiving Protocols below) can also be used as an excellent means of providing education and anticipatory guidance to parents and families, especially when provision of information with skill-building must be completed over a long hospitalization or by several staff members (Butt et al., 2013).

Family Presence and Participation in Procedures

One of the fundamentals of FCC is the belief that the family is an active member of the caregiving team right from admission. Members of the caregiving team are *not visitors*. Parents are not asked to leave for rounds or procedures but are integral members of the caregiving team; they are invited to be as involved during procedures as they feel comfortable with; the degree of involvement would vary from parent to parent and family to family (Axelin et al., 2010; McGrath, 2011). Parents need to have enough information to feel welcome and supportive of their infant during procedures to be present (Palomaa, Korhonen, & Pölkki, 2016). Presence during resuscitation is one of the areas where more and more NICUs are providing families the support to be present and supportive to their child. However, this means someone from the healthcare team needs to be supportive of parents during the event (Gasparini et al., 2015). Staff members may resist including families in these interventions because of the degree of risk to the infant. Nurses must also take into consideration that even though parent participation might lead to short-term physiological losses for the infant, these losses might outweigh the long-term gains for the family and make a decision with the family that is in the best interest of the infant. Established protocols and education of both staff members and parents help with the transition to increased parental participation in the NICU (Mundy, 2010; Raiskila et al., 2017).

Supporting Families With Caregiving Protocols

Critical pathways and caregiving protocols have been developed to aid in the organization and evaluation of nursing assessments and interventions with children and families. These pathways help promote continuity of care and aid the nurse in prioritizing the needs of the child and family. They are outcome-oriented and provide an excellent means of documenting nurses' actions. They can be used to enhance interaction between parents and their preterm infant. The pathway serves as a means to educate parents about the changing needs of their developing preterm infant. Implementation of the pathway increases parents' knowledge and responsiveness to their infant's behavior and helps parents develop independent, cue-based caregiving skills with their infant (Tooten et al., 2012; Zelkowitz et al., 2011). Other pathways have been developed with five areas of emphasis: 1) environmental organization; 2) structure of caring; 3) feeding (all of which relate more to the infant); 4) family involvement; and 5) family education (which relate more to the needs of the family). Involving families in the development and testing of these protocols is important (Celenza, Zayack, Buus-Frank, & Horbar, 2017). Outcomes for infants include physiological stability, behavioral organization, and establishing predictable behavioral patterns; outcomes for the family include enhancing social support, increasing knowledge, and increasing involvement in the infant's care while preparing for discharge (Boykova & Kenner, 2012; McGrath, 2012). Critical pathways also are an excellent means of providing education and anticipatory guidance to parents and families, especially when teaching must be done over a long hospitalization or by several staff members.

Family Integrated Care

Recently the concept of delivering supportive care to the infant and family in the NICU has been reconceptualized as the Family Integrated Care (FICare) model in which parents provide all care for their infant, except the most advanced medical care, with support from the healthcare team (O'Brien et al., 2015). First introduced in Canada, the premise of this model is based in the fact that it is essential that parents are an integral part of the healthcare team. Parents who participate in this program are required to be in the NICU at least 6 hours a day, 5 days each week to provide care to their infant. Parent participation is facilitated by parent education programs that provide the content and facilitation for parents to be successful in providing complete care to their infants. Educational tools and self-directed learning approaches are utilized to increase parental confidence and decrease parental stress (Bracht et al., 2013; O'Brien et al., 2015). The educational programs encompass materials that empower parents to recognize infant cues and behaviors through engagement in their unique role in their infant's life. Ongoing dialogues among the team are encouraged to accommodate a variety of learning styles and remain flexible to adapt materials to meet the diverse needs of families (O'Brien et al., 2013). The use of veteran parents as support partners also facilitates parent participation in FICare (Galarza-Winton, Dicky, O'Leary, Lee, & O'Brien, 2013). Staff nurses who participated in FICare also report high levels of satisfaction although there was a learning curve in becoming a "coach" to parents delivering the care to their infants (Macdonnell et al., 2013). The outcomes of this research have been very positive with more studies now in progress in both Canada and the United States. One limitation of the research to date is the high refusal rate (>50%) related to the degree of parent presence required if parents choose to participate. In addition, there are no true measures of degree of parent engagement in the studies and there is yet little support for whether this dose (6 hours a day for 5 days each week) is the right dose to achieve the desired outcomes. While more research is needed to better understand how to best implement FICare, this model of care is definitely propelling caregiving that increases the family's true partnership in the care of their infant in the NICU.

Family Conferences

Family conferences can be used to evaluate the intervention strategies and how well they were able to meet the family's goals. Collaboration during conferences allows all present the opportunity to examine individual perspectives and goals while negotiating and reevaluating strategies to increase satisfaction with the

treatment plan (Brett et al., 2011; McCormick et al., 2008). The type of information communicated is also an important consideration. Healthcare professionals have often provided families with a lot of information about their infant in the here and now; what is sometimes missing is the "so what" of that information (Fox et al., 2005; McGrath, 2007a; Morey & Gregory, 2012; Reis et al., 2010). The result of this type of communication is that parents are not always provided with all the information they need to understand the whole situation for their child now and in the future so that appropriate participation in decision making can occur (McGrath & Hardy, 2008).

Facilitating Transfer to Another Facility

If the infant is transported from another facility or being transferred to another hospital, parents need time to be with their infant prior to the move and should go on the transport with the infant whenever possible (Fidler & McGrath, 2009; van Manen, 2012). These brief interactions before transport reduce anxieties about the status of the neonate and promote bonding and attachment behaviors (Aagaard et al., 2018; van Manen, 2012). Occasionally, the mother's condition is unstable and she or a family member cannot be present in the NICU. Instant pictures can be taken and given to the mother as soon as possible. Some NICUs are also using video conferencing to keep families better connected to their infant.

The number of nursing or medical personnel in nondescript surgical scrub outfits who interact with the parents can be overwhelming. Therefore, introductions by name and position are important to families, and personnel should wear name tags to help further identify each staff member. Many institutions have adopted a primary nursing style of care where the number of caregivers is limited to a small group of professionals to increase consistency of caregiving and information-sharing. Families often feel more secure knowing that one nurse or team of nurses direct their baby's nursing care throughout the hospitalization and this allows a trusting, collaborative relationship to be established (Box 35.7). A friendly approach facilitates open communication and demonstrates openness and approachability.

Using language that invites participation is also important (Box 35.8). The primary nurse can act as liaison between the family and the healthcare team. The liaison ensures that information about the infant's current condition, any changes in condition, and long-term outcomes for the infant are communicated to the family. The liaison role becomes essential if the infant is transported back to a community hospital or to another unit in the same facility (Aagaard et al., 2018; Fidler & McGrath, 2009; van Manen, 2012). Parents need to know what to expect in the new unit and to understand how this environment is now actually better suited to meet the changing needs of their infant. Otherwise, parental mistrust may develop (Aagaard et al., 2018).

Preparing for Discharge. As nurses prepare the infant for discharge from the NICU, it is important that the parents feel prepared to care for their infant (Bos et al., 2018; Boykova & Kenner, 2012). Building on the already established relationship, parents can be provided one last boost in confidence by allowing them to room-in with sick newborns before discharge (Peyrovi et al., 2015; Toral-López et al., 2016). Structured education has also been found to increase parent confidence and caring knowledge prior to discharge, which could make the transition from hospital to home easier for families (Bos et al., 2018; Lopez, Anderson, & Feutchinger, 2012; Moradi et al., 2018; Shieh et al., 2010). Parents feel secure knowing that nurses are close by if they are needed. This process also allows parents the assurance that they can care for their babies adequately.

Box 35.7

PRINCIPLES OF FAMILY–PROFESSIONAL COLLABORATION

Family–professional collaboration accomplishes the following:

- Promotes a relationship in which family members and professionals work together to ensure the best services for the child and family
- Recognizes and respects the knowledge, skills, and experience that families and professionals bring to the relationship
- Acknowledges that the development of trust is an integral part of a collaborative relationship
- Facilitates open communication so that families and professionals feel free to express themselves
- Creates an atmosphere in which the cultural traditions, values, and diversity of families are acknowledged and honored
- Recognizes that negotiation is essential in a collaborative relationship
- Brings to the relationship the mutual commitment of families, professionals, and communities to meet the requirements of children with special health needs and their families

Source: Adapted from Institute for Patient- and Family-Centered Care. (2017). *Advancing the practice of patient- and family-centered care in hospitals: How to get started*. Bethesda, MD: Author. Retrieved from http://www.ipfcc.org/resources/getting_started.pdf

Box 35.8

LANGUAGE THAT FACILITATES COLLABORATION

"Do you prefer us to call you by your first name or your last name?"

"Here's what I'm thinking, but I'm wondering how this will work for you."

"Tell me how I can help you."

"Our institution usually does it this way. Would that work for you?"

"These are the things I plan to provide for your child today. Would you like to provide some of these activities?"

"What goals do you have for your child's care?"

"How does your child look to you today?"

"Do you have any questions or suggestions about your child's care?"

"This sounds important; help me understand your concern."

"Who would you like to have included in discussions about your child's care?"

"Let's talk about how much you want to be consulted."

Source: Adapted from Fox et al. (2005).

Many times the neonatal intensive care hospitalization is the beginning of chronicity for the infant and the family (Bally et al., 2018). Parenting a chronically ill child is qualitatively different from parenting a normal child. Nurses must promote the parents' and family's role as caregivers for the child by determining the

family's mode of coping and supporting those strategies while promoting family adaptation to the chronic illness and parent learning of self-management skills (Hägi-Pedersen et al., 2017). A major goal of care for these families is to integrate the child back into the family unit rather than to make the child with a chronic illness a "special nucleus" that becomes the only priority or focus of family needs (Nightingale, Wirz, Cook, & Swallow, 2017).

FCC of an infant or child with any chronic illness is based on the premise that the family is the main source of support and caregiving for the child. Thus, FCC can be achieved through specific nursing strategies aimed at creating opportunities for families to use their own strengths and abilities to meet the infant's and family's needs (Ahlqvist-Björkroth, Boukydis, & Lehtonen, 2013; Bally et al., 2018). Ultimately, family-centered interventions empower families to develop and maintain healthy lifestyles, leading to overall improvement of the family's quality of life.

Providing Support for Parents and Families

Parent networking can be a vital tool for promoting parenting. Knowing that other families have survived this crisis can be reassuring. Support groups are generally helpful; however, they are not appropriate for every situation (Al Maghaireh et al., 2016). Some couples need counseling so they can feel more comfortable with decision making and participation in care. The primary nurse plays a key role in assessing signs that the family is not coping and needs therapeutic counseling. Support groups or counseling help families examine problems objectively and learn alternative behavior for adaptive coping (Ardal et al., 2011; Hall, Ryan, Beatty, & Grubb, 2015). The nurse also can assist parents in identifying additional means of support. Ideally, parents should be permitted to define their "family" as needed to provide support during this crisis, allowing family members to be present as unit policy dictates. Grandparents, extended family, neighbors, and friends may constitute this group (Stefana & Lavelli, 2017).

Grandparents are a source of support for many parents. However, grandparents may be forced into an uncomfortable role by seeing their own child in pain without a way to relieve that pain. Understanding intergenerational dynamics is important in providing the best support to families. Grandparents are also trying to cope with this new crisis and may relive their own birthing experiences, which could result in associated anxieties and prevent them from being available to provide support for the parents (Frisman, Eriksson, Pernehed, & Morelius, 2012). Extended family members may be more helpful if discord exists between grandparents and the nuclear family (Greisen et al., 2009). Friends of the family can be an asset if they are effective listeners. They can offer to provide transportation for the mother and child care for siblings or they can take over housekeeping chores to help alleviate family responsibilities. Just having someone to make telephone calls to other friends and family to update them on the infant's condition can be a great relief for the family.

Social workers involved early in the hospital stay provide parents with an objective person to discuss caregiving options and provide contact with community resources. Families are often reluctant to express dissatisfaction with their child's care to nurses. Social workers can help parents express concerns without fear of retaliation against their child. Clergy provide spiritual support for a family. Families often turn to religion for comfort and support at a time of crisis. It is important to offer these resources to parents and to provide the appropriate privacy to exercise their religious freedom. Recently it has been recommended that we reconceptualize the neonatal intensive care environment to be the neonatal intensive parenting unit (NIPU; Hynan et al., 2015; Hall et al., 2017). This reconceptualization places the parent with the infant at the center of caregiving. The evolution of caregiving such that care providers are for the support of parents and infants is one that needs increasing support as the family is the constant and the long-term care provider for the infant.

PARENT AND STAFF EXPECTATIONS

When parents have a sick infant in the NICU, they have expectations. They expect excellent medical and nursing care for their child (Latour et al., 2010). They expect accurate and timely information throughout their child's illness, and they expect to be involved in decision making about the infant's care (Hardy & McGrath, 2008). They expect that this relationship that is developing with the healthcare team will be a partnership and that the partnership will be honored in every interaction. The medical and nursing staff members, working as a team supportive of each other and the family, have the ability to instill confidence in parents through this partnership (Raines & Brustad, 2012). Parents develop advocacy skills through collaborative communications with the nursing and medical team (Hardy & McGrath, 2008; McGrath, 2011; McGrath & Hardy, 2008; Morey & Gregory, 2012). Conversely, members of the medical and nursing staffs have expectations of the infants and families within this partnership related to the care of the infant. Expectations for the family may include regular presence and participation in caregiving, respecting the routines of the NICU setting, and sharing information that may be helpful in the care of the infant (Meiers et al., 2007). Sometimes these expectations are unrealistic. For example, the staff may expect parents to be present and more active in caregiving more often, even though the parents live far from the hospital, have other children, must return to work, and have other responsibilities that may prevent more frequent presence and participation in caregiving (Craig et al., 2015). Parents may also feel there is no role for them in the NICU if a collaborative partnership has not been established and the environment is not welcoming (Klegerg, Hellstrom-Westas, & Widstrom, 2007; Reis et al., 2010). Staff expectations for the infant may include wanting the infant to nipple-feed more often or be weaned from oxygen faster. It can be distressing to parents to think that the medical staff is not pleased with their infant's progress, even though this attitude may not be verbalized. For this reason, incongruities should be avoided both in actions and in communications (Hardy & McGrath, 2008; Reid, 2007). It seems reasonable to assume that parents who are partners, well informed, and participating in the care are less likely to experience these concerns (Brett et al., 2011; Hopwood, Clerke, & Nguyen, 2017).

Staff members' attitudes are an important part of the development of positive parenting (Box 35.9). Staff behaviors and attitudes can inhibit or encourage parenting skills. Conflict about parenting roles can exist between parents and staff members and this conflict may escalate into a struggle for control. Parents may view staff members as acting as the infant's parents, or the infant as belonging to the staff because staff members provide most of the care (Epstein et al., 2013). The staff members' pet names for the neonate further reinforce parents' fears. Nursing staff can help the family by encouraging them to personalize the infant's care and then following their lead with naming and dressing. Bringing in clothes, toys, and pictures of other family members and making recordings of family voices are ways parents contribute to caretaking.

Nurses who care for families need to provide support and promote the family as a unit; however, overinvolvement of nurses can be detrimental to the family unit. Establishing appropriate relationships with families in our care can sometimes be difficult. It

Box 35.9

KEY CONTENT OF FAMILY-CENTERED TRAINING PROGRAMS FOR HEALTH PROFESSIONALS

- Principles of family-centered care
- Cultural competence
- Child development
- Family systems
- Fostering communication with children and families
- Building of collaborative relationships with families
- Support for and strengthening of families in their caregiving roles
- Impact of hospitalization, illness, and injury on children and families, including the impact of healthcare costs on family resources
- Support for the developmental and psychosocial needs of children and families through hospital policies and programs
- Function and expertise of each discipline in the medical setting
- Multidisciplinary collaboration and team-building
- Ethical issues and decision making
- Community resources for children and families

Source: Adapted from Institute for Patient- and Family-Centered Care. (2017). *Advancing the practice of patient- and family-centered care in hospitals: How to get started*. Bethesda, MD: Author. Retrieved from http://www.ipfcc.org/resources/getting_started.pdf

Box 35.10

BEDSIDE CAREGIVER BEHAVIORS THAT MAY BECOME BARRIERS TO POSITIVE PARENTING

- Infant "belongs" to the nurse and the NICU rather than to the family; nurse refers to assignments or primaries as "my babies."
- Family is not considered a member of the caregiving team; for example, they are asked to leave for rounds and shift reports.
- Family is not asked about the characteristics of their infant or included in discussions related to the infant. Families are not seen as the experts on their infant. They are talked about rather than talked with.
- Care is task-oriented and staffing is acuity-based rather than based on meeting the needs of families. Families are not invited to participate in the child's care.
- Infant's schedule belongs to the nurse and the NICU rather than to the family, so that feeding and caregiving might occur when the family is unavailable to participate. Scheduling is inflexible.
- Family is seen as an adjunct to infant care. They are not the client or patient. Spending time with families is not considered a priority but rather a luxury. Spending time with families is not seen as essential to providing care for the infant.

Sources: Data from Institute for Patient- and Family-Centered Care. (2017). *Advancing the practice of patient- and family-centered care in hospitals: How to get started*. Bethesda, MD: Author. Retrieved from http://www.ipfcc.org/resources/getting_started.pdf; McGrath, J. M. (2007a). Family caregiving: Synchrony with infant caregiving? *Newborn and Infant Nursing Reviews, 7*(1), 1–2. doi:10.1053/j.nainr.2006.12.003

is necessary to identify inappropriate nursing behaviors and correct them. Educating the nursing staff about the parenting process facilitates identification of inappropriate nursing behaviors (Box 35.10). The education can be initiated during orientation of new staff members and reinforced at intervals with continuing education workshops on the subject. Nurses must provide support while always acknowledging the boundaries of the family. Some families build walls and are so private about family matters that it is difficult to obtain enough information to meet family needs, whereas other families become overly dependent on the nursing staff, needing their support at every moment. Interventions that promote independent family decision making include the following (IPFCC, 2017):

- Respecting the family as a unique unit
- Providing unbiased care to all families
- Providing as much continuity in the care provider as possible to promote family strengths
- Allowing the family to determine the implementation of the plan of care

With adequate staffing, nurses can better promote parenting in the NICU. Overworked nurses can become frustrated and stressed, overwhelmed by their own anxieties. These feelings may impede their ability to interact calmly and therapeutically with a fragile family unit. Nursing management considerations should include provision for adequate staffing to allow nurses the time and emotional energy to meet the needs of parents in crisis. Patient assignments should be evaluated not only for the technical care an infant requires but also for the psychosocial demands of the family. Institutional policies should be carefully evaluated as to how they meet the needs of families. Rationing or missed care must be regularly evaluated and considered such that optimal care is delivered to all infants and families (Tubbs-Cooley et al., 2017). FCC activities are more likely to be among those caregiving tasks that are missed, such as family teaching, breastfeeding education, discharge planning, holding, and SSC.

SIBLINGS

Siblings have needs because they are an important part of the new infant's life. Sibling visits may help relieve anxieties and make the birth a reality. Siblings have a variety of responses to a newborn's arrival in the home, especially after a lengthy hospitalization. Family routines are disrupted by a "normal" birth and are further disturbed by an admission to the NICU and then again at the time of discharge (Peyrovi et al., 2015). Siblings may feel displaced while parents are at the NICU participating in the caregiving of the ill infant. Siblings are often left with babysitters when they have rarely had experience with caretakers outside the immediate family. Fathers who may be uncertain about their family role may embrace their familiar work role and spend more time on the job. In these ways, routines are disrupted and parents are less available for their other children. These feelings may result in a variety of acting-out experiences.

The birth of a new baby precipitates a family upheaval and the need for a realignment of relationships and positions within the family constellation. Becoming a sibling is known to be a stressful or "crisis" experience for young children and can have an effect on their mental, emotional, and social development. The birth of a preterm or critically ill neonate who requires intensive care constitutes a further crisis for parents and consequently disrupts the equilibrium of the family system (Morrison & Gullon-Rivera, 2017; Stefana & Lavelli, 2017). Parents are reported to experience

feelings of anxiety, grief, fear, anger, and guilt in response to the unanticipated events. Siblings are also affected and may experience helplessness, powerlessness, guilt, and anger in addition to the disruption of their daily routines and separation from their parents. The siblings may feel very alone because their worried parents are preoccupied with the newborn baby. Siblings feel like the forgotten family member at the very time they need attention most (Morrison & Gullon-Rivera, 2017).

Addressing the needs of the families of hospitalized patients has gained acceptance and support among nurses since the advent of the concept of FCC (IPFCC, 2013b, 2017). All members of the family, parents and siblings, may exhaust their coping strategies and feel unsupported by those who are usually available emotionally and physically. The philosophy of FCC in the NICU is reported to encourage not only parent participation but also involvement of the well sibling or siblings in the family process. This involvement allows children to see their new sibling and to feel as if they are a part of the family process. Feelings of isolation may engender fantasies about what is taking place in the NICU. At any age, it is easier to cope with reality than with what can be imagined. Increasing numbers of hospitals are encouraging the participation of children at a sibling's birth, sibling contact with the infant at birth, sibling contact with the infant on the postpartum unit, and sibling visits in intensive care nurseries.

For nurses facing these challenges, the philosophy of FCC can provide a firm foundation in striving toward excellence in the practice of caring for children and families (Agency for Healthcare Research and Quality, 2013; IPFCC, 2018; Provenzi et al., 2015; Stefana & Lavelli, 2017). The development of a sibling–infant bond is vital to establishing and enhancing the relationship within the family unit. Holistic care surrounding childbirth may set up patterns or pathways that dramatically affect subsequent family interactions.

Some families feel they cannot be part of the care team. They either do not desire to provide care or cannot do so. Sometimes there is a tendency to label them as noncompliant with what the healthcare professional believes the family should do or how they should act. Before a label is used, it is important to find out from the parents why they do not want to participate. Is it because they fear they will hurt the infant? Is it because they want to just be parents and not be responsible for the care? Is it a lack of understanding of what is being asked of them? Based on their response, an individualized plan of care can be developed. For example, for the parent that is fearful about providing care, the healthcare team can provide education, psychological support, and be present to support caregiving activities. The key to success is to talk to the family, listen to their concerns/perspectives, and then tailor a plan to increase their participation as a care team member.

Sibling Visitation to the NICU

Sibling visitation in the hospital after the delivery of a newborn has become common practice. However, limited recent research exists that examines the consequences of permitting and prohibiting sibling visits in the NICU, despite the argument that sibling involvement is consistent with the concept of family-centered perinatal care. Early studies of NICU sibling visitation programs provided valuable descriptive data on siblings' responses to the sick neonate (Griffin, 2013). NICU visits provided an opportunity for the older brother or sister to see, touch, and talk to the newborn. This exposure was reported to help the children integrate the reality of the experience, to prepare for the possible loss of the newborn, and in some cases to reverse regressive behavior that had begun during the newborn's hospitalization. However, the findings of these studies reflected the perceptions of providers and not necessarily those of the parents or siblings (Gooding et al., 2011). More research is needed in this area. Some NICUs restrict sibling visitation during respiratory syncytial virus (RSV) season, whereas some do not have a strict policy for how visiting might still occur during this time of the year. The same is true for varicella exposures and how to safeguard infants (Kellie, Makvandi, & Muller, 2011). Again, more research is needed in this area.

Implications for Practice

Nurses have a unique opportunity to support the development of positive sibling relationships in the NICU environment. Evolving models of comprehensive care no longer overlook or delegate the care and needs of the whole family. Research on the families of NICU neonates has demonstrated parents' desire for a family-centered approach to care (Miyagishima et al., 2017). Siblings are an integral part of any family and their adjustment or lack of adjustment to the birth of a newborn greatly affects the well-being of the whole family. Siblings' adjustment to the once-sick infant needs further exploration.

When the birth of a sibling is further complicated by the baby's being ill or at risk, professionals caring for the baby are in a position to reassure parents that siblings will respond to the neonate in various ways based on each child's personality, age, and interests. Professional reassurance can help parents realize that siblings cannot help feeling angry and displaced by the baby. The parents' ability to accept their older children's competitive feelings and yet continue to love them helps those children to integrate ambivalence. Support through this ambivalence facilitates acceptance of the infant and the infant's incorporation into the family. Increasing parents' knowledge about promoting positive sibling relationships through parent education programs may influence parental attitudes, thereby enhancing future sibling relationships. In response to consumer demand, many hospitals have implemented sibling visitation and educational programs. This preparation can help siblings deal with the realities of the experience. Special attention from the NICU staff can also help siblings feel recognized, supported, and appreciated during this time of stress. Encouraging the sibling to gently touch and talk to the infant and allowing gifts of toys or even a drawing of themselves to be kept with the baby are activities that may foster attachment and growing connection with the newborn.

The death of a sibling usually has profound and lasting effects on surviving children. Surviving siblings, however young, may need some evidence that the baby existed—a visit to see the ill newborn in the incubator, a photograph, or a chance to participate in the funeral. Regardless of the child's age, it seems that the level of care offered to these siblings is crucial to determining the psychological and life adjustment of the bereaved child. Nurses need to be alert to the range and depth of childhood reactions. Many research findings discussed here can serve as invaluable guides to help NICU nurses promote and facilitate effective sibling interactions and positive involvement between the sick neonate and the siblings. An appropriate environment in which nurses can assist children in coping with the profound changes that affect the sibling bond should also be provided, because such efforts help siblings fully integrate this major event into their young lives.

Environmental Effects

A quiet, comforting atmosphere with low lighting helps calm both infants and their families. External stimuli in the NICU must be controlled; unnecessary stimuli aggravate these infants' already overwhelmed immature nervous systems and loud monitor alarms and excessive staff noise can be upsetting and unnerving to parents (D'Agata & McGrath, 2016). In general, the equipment is

overwhelming to families and makes them feel like outsiders. Their discomfort inhibits interactions with the infant and delays their participation in caregiving. Researchers suggest changes in the technology of the NICU, such as use of different kinds of alarm signals with diminished volume; wireless, handheld information terminals; and remote monitoring. Some of this technology is already appearing in the NICU. The technology used in the NICU must be continually reevaluated and designed with a parent- and consumer-based perspective (D'Agata & McGrath, 2016). Achieving a balance between the high-technology environment and the need that parents have to touch their infant frequently helps foster parental self-confidence. This balance must be a priority for the neonatal nurse.

Recommendations for single rooms in the NICU and other acute care areas throughout the hospital setting are now included in the 2006 Guidelines for the Design and Construction of Hospital and Healthcare Facilities (Ninomura, Rousseau, & Bartley, 2006). These guidelines are based on several significant research studies where single rooms throughout the healthcare setting were found to offer higher occupancy rates, reduced transfer costs, and lower labor costs, even when the cost of new construction was calculated into the equation (McGrath, Samra, & Kenner, 2011; White, Smith, & Sheply, 2013).

In addition, hospital-acquired infection and medication errors were reduced in these settings. Most patients and families also report better communication with healthcare professionals in single rooms because the provider often spends more time, answers questions more thoroughly, and is more compassionate and caring. Patient length of stay has been documented as shorter in private single rooms, which also adds to the decrease in costs (Please see the 2006, Updated Guidelines for the Design and Construction of Hospital and Healthcare Facilities). This movement to single rooms in the hospital setting is also important for compliance with the patient and family privacy requirements under the Health Insurance Portability and Accountability Act of 2003, which includes speech privacy rulings.

So how do these guidelines affect the NICU? There is little research directly related to the effects of neonatal single-room design. Most units across the United States have always been equipped with a few isolation rooms that have been used for infants with highly infectious diseases and, more recently, to isolate extremely low birth weight preterm infants who appear to be most overstimulated by the big open room environment of the NICU. With new construction, and a greater emphasis on individualized family-centered developmentally supportive care, more units have added more of these single rooms and some units have chosen to move to an entirely single-room design (Baker & McGrath, 2010).

Research to support a less stressful NICU environment with lower lights and less noise and activity has demonstrated shorter lengths of stay, decreased iatrogenic effects, and increased deep sleep and alerting behaviors in the infant, which may provide greater opportunities for more normal cognitive development. Moreover, in changing the environment to meet the needs of infants and families, the less stressful environment is oftentimes more positive for caregivers and should have a positive impact on patient outcomes and a decrease in medication errors (Domanico et al., 2010; Pineda et al., 2012). The challenge in providing care in these designs is finding a balance between the needs of infants, families, and caregivers in the NICU. This may be best achieved in a single-room design, where areas in the unit can be designed to meet the needs of those who use them most, yet allow others to adjust their individualized areas or rooms to meet their needs (Baker & McGrath, 2010). Evidence-based design standards for the NICU do exist and should be considered with any remodeling or new construction project (Jones, Peters, Rowe, & Sheeran, 2016; White et al., 2013). These guidelines should be used as a standard, especially when data are needed to support the need to invest upfront in more space, better traffic patterns, multiple kinds of lighting, and noise reduction materials. Paying attention to design is especially important for vulnerable infants who are at risk of developing disabilities. Research data also exist and should be used to support the need to choose colors and textures that increase health and well-being for all who interface in healthcare settings. For staff to transition to and work with ease in single-room designs, they must have access to and become comfortable with central monitoring and communication systems that provide them knowledge about patient status even from remote locations. Work areas for nurses must also be near the private rooms and allow for interaction and teamwork among staff. More research is needed in this area and should be a focus for the future.

SUMMARY

The birth of any infant produces tremendous change in the lives of each member of the family. Normal adaptation can be complicated by the birth of a premature, critically ill infant, or one with congenital anomalies requiring admission to the NICU. If the family does not have adequate coping strategies or resources, this crisis has the potential to produce much role stress and strain which ultimately can weaken or destroy the family unit. The nurse plays an integral role in supporting and guiding the family to appropriate resources and services. By promoting adaptive roles, the nurse can ensure an intact family unit after the crisis of intensive care.

EVIDENCE-BASED PRACTICE BOX

John Jones was born at 33 weeks' gestation. The nurses described him as a typical preemie with respiratory distress syndrome and intermittent apnea and bradycardia. He required continuous positive airway pressure (CPAP) for several days and then hood oxygen for a week. After being weaned to room air, he was moved to the transitional nursery, where he stayed for another week until he mastered sucking, swallowing, and breathing. John's mother was present often and participated in caregiving. Mrs. Jones kept John supplied with breast milk and the latest drawings from his two sisters, Suzie, age 6, and Becky, age 4. John's father was present in the NICU irregularly. He tried to make the time to be present on his way home from work but did not take an active role in caretaking. He said that he was afraid to hold John but that he would as soon as John got bigger and stronger. John was a cuddly little guy who had an uneventful recovery and was discharged after 3 weeks in the NICU.

Several days before discharge, John's mother confided in his primary nurse that she was at the end of her rope because her husband was working longer hours and her daughters were acting up in ways they never had before. Becky had demonstrated regression behaviors of bed-wetting and thumb-sucking. She had also started carrying around her "blankie" again, something she had stopped doing long ago. Becky was particularly

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EVIDENCE-BASED PRACTICE BOX (*continued*)

close to her mother, and after her mother's daily trips to the NICU, Becky would hit her mother, crying, "I hate you! I wish the baby would go away!" Mrs. Jones said that when she tried to console Becky, the child ran and hid under her bed, crying, "Leave me alone! You only love that baby!" If that weren't bad enough, Suzie had begun waking up with stomach aches and refusing to go to school. Suzie had always loved her teacher and classmates and now was frequently in trouble for misbehaving in class. When Mrs. Jones would make Suzie go to school, the little girl would cry and say, "I hate that baby! I'd like to run over him with Daddy's car!" Mr. Jones had withdrawn from family life and was spending long hours at work. Mrs. Jones was beside herself.

The nurse was able to reassure Mrs. Jones that the behaviors of her husband and daughters were typical. Although this reassurance didn't immediately alter the situation, at least Mrs. Jones knew that many families respond to NICU hospitalization in this way and that, given time, the family would reestablish equilibrium. Mrs. Jones was encouraged to take the weekend off from her NICU caregiving routine. She was able to spend a couple of special days with her daughters and engage her husband in life outside the worries of the NICU.

However, this did not provide Mrs. Jones with emotional support or help with her feelings of being overwhelmed and depressed. The nurse was able to listen to her concerns and then put her in touch with a parent organization that had been formed to help support families through the transition home. The parent organization offered peer support from parents who had been through the experience. They were also able to help Mrs. Jones place the experience in its proper perspective.

The girls had enjoyed their weekend with their mother and were in a better frame of mind for the homecoming. Peer support helped Mrs. Jones so that she could in turn be available to her family. John was about ready for discharge and had progressed normally. Once John was home, Mrs. Jones included the girls in the baby's routine as much as possible by asking them to get his diapers and having them feed their dollies while she fed John. Suzie brought pictures of John to school for show and tell, and after Mrs. Jones called to speak to the teacher to explain the disruptions at home, Suzie gradually quit misbehaving. Becky continued to have problems with thumb-sucking and bed-wetting for several months while incorporating John into the family and establishing a new family routine.

PARENT VOICES

Ali Dunn

Allowing someone you have just met to care for your tiny, sick baby is one of the hardest things a parent can do. Having to rely on the nurses to tell me how my babies were doing, to show me how to care for them, and to give me permission to hold them was heartbreaking, as I had waited so long to be a mother. But over the days and months that my babies stayed in the NICU, the good nurses helped me realize that the nights spent apart or the feeds you missed did not diminish your mothering heart. The good nurses empowered me to change tiny diapers without assistance, so for brief moments I could feel like a normal parent. The good nurses waited for me to do the next feed, even if it meant putting themselves behind schedule, so I could momentarily forget about the wires and tubes, the monitors and machines, and just enjoy a nurturing moment with my child. The good nurses know that even though parents don't always say it, we are forever grateful to them for loving our children when we were not there, and for caring for our babies when we could not.

Jennifer M. Driscoll

Both of my children were both prematurely, Lilian Hope in 2007 and Aidan Patrick in 2013. Lily spent just under a month in the NICU, and Aidan only a few days. Being discharged from the hospital with Lily was probably one of the most nerve-racking days of my life. Fortunately, when Aidan came home, I had that "mom" confidence, and having been in the NICU before, I knew what to expect.

I personally need a lot of information and dialog when it comes to caring for my children. I learned that I need to visualize what this new "normal" would look like and have a clear understanding before taking on this big change. I remember asking tons of questions, taking advantage of infant CPR classes, apnea monitor classes, reading all the literature from the hospital, and even staying over in the hospital NICU with Lily the night before she was discharged for practice. I'm a rule-follower by nature, so when coming home with Lily, I tried to instill the rules and guidelines that the NICU staff suggested. These were things like limiting the number of visitors, having hand sanitizer at every sink, no touching the baby until they washed their hands and used hand sanitizer, not taking the baby out in public if you

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can avoid it, and more. And I listened, which was great and tough. I felt lonely and nervous because I was a new mom caring for this 3 lb, 11 oz baby that had just entered our lives so abruptly.

Home became a learning experience. Where do I buy preemie clothing, diapers, and this special formula? I don't think I was ever even in a Babies R Us but to register for my shower, Amazon Prime wasn't even a thing in 2007. We went day by day, spending time doting on her, learning about her, and trying to comfort and nurture her as best we could. Home brought new challenges like severe reflux, visiting nurses waking her up from nap times, severe lack of sleep, a husband that worked a swing shift and caring for this little infant alone, a dog that barked every time she cried, and much more. We learned to roll with the punches, stay flexible, but yet always be in tune with what the baby was "telling" us.

Katie Reginato Cascamo, MA

Neonatal staff who truly transform families begin with their own wellness first. The metaphor of putting on one's own breathing mask before caring for others is more critical than ever before in healthcare. As healthcare providers become more whole and fill their own emotional bucket, they effortlessly pour that out to families in crisis. As clinicians grow as healthcare leaders, they build the container skills for families who will need to take a leadership role in their family. Even the most difficult families respond well to healthcare providers who have invested in their wellness and leadership development. As you engage in your work holistically, you are equipping parents to take the initiative to transform their lives. So, take that hike. Do yoga. Develop a spiritual practice. Participate in wellness programs. Create meaningful connections with your coworkers. Care first for yourself so we can depend on you to care for us.

Our NICU was organizationally healthy and committed to transforming our lives. Our NICU served a large geographic area of nine counties and we lived 100 miles away over a snowy pass in the middle of winter. We did not trust our local, rural hospital primarily due to the lack of interpersonal development of the staff. The day after our NICU discharge and our return home, our son desaturated to 82% O_2 that I believed had to do with a 3,000-foot elevation change. I took him to our local dysfunctional emergency room simply because I had no other choice and we spent three more days in the hospital that redefined my mission to transform dysfunctional healthcare. The local healthcare staff refused to believe that the elevation change played any role in his desaturation and drastically changed how we perceived the community we called home. One year later we moved to a healthy, thriving community with world-class healthcare solely based on our experience in a healthy, engaged healthcare system and its counterpart, a toxic, dysfunctional healthcare system. Through our relocation to a community with high-quality healthcare came a world-class education system, commitment to the integration of children with special needs into society, and my ability to retrain for a job in healthcare practice administration.

All parents that come into the NICU have a story. Be willing to listen to our story and discover our strengths. Most of us have professional experience and are equipped to care for our babies. We are often fearful of touching our babies and experiencing trauma and it is the very act of learning how to care for our babies that heals us. The best amenities for families are parent-led resources. The world's best, most empathetic resources are those resources written for parents, by parents who have experienced a NICU stay. Our resources are very high quality, have the oversight of neonatal professionals, and are trusted by healthcare systems.

Integrating families into the care processes of the NICU is a win-win for everyone involved. For nursing staff, investing in our skill development is one more item to check off the healthcare checklist. As we learn to do nonessential tasks such as diapering, feeding, and dressing, we help you manage your workload better. We want to care for our baby and need guided instruction so we can take over nonessential tasks. Most importantly, when we leave the NICU, the skills you are teaching us are skills we will need when we return home. As we learn these skills, we become leaders in our families and we make sure that we engage in ongoing developmental therapies for our children through early intervention. As we broadly became the primary caretakers from birth throughout childhood, we are ensuring successful developmental outcomes of our preemies.

ONLINE RESOURCES

Institute for Patient- and Family-Centered Care. Institute supports the advancement and practice of patient- and family-centered care. Many resources are available to professionals and families on their website to support partnerships and collaborations at all levels of healthcare. Retrieved from http://www.ipfcc.org

National Center for Cultural Competence. The primary focus of this center is increasing the capacity of health and mental health programs. Resources are available to support the design, then implement and evaluate culturally and linguistically competent service delivery systems. Other resources include self-assessment tools, publications, on-site training, and education. Retrieved from https://nccc.georgetown.edu/

NICU Family Support Program-March of Dimes. Retrieved from http://www.marchofdimes.com/baby/inthenicu_program.html

NIDCAP Federation Resources for Families https://nidcap.org/en/families/resources-3/

Preemie Voices. Retrieved from http://www.preemievoicesbook.com/

Preemieworld. Retrieved from https://preemieworld.com/

Preemie Parent Alliance is a network of organizations offering support to families of premature infants. We are the only professional association for NICU Parent Leaders in the United States. Retrieved from https://preemieparentalliance.org/

REFERENCES

Aagaard, H., Lall, E. O. C., Ludvigsen, M. S., Uhrenfeldt, L., & Fegran, L. (2018). Parents' experiences of neonatal transfer. A meta-study of qualitative research 2000-2017. *Nursing Inquiry, 25*, e12231. doi:10.1111/nin.12231

Agency for Healthcare Research and Quality. (2013, June). *Guide to patient and family engagement in hospital quality and safety*. Rockville, MD: Author. Retrieved from http://www.ahrq.gov/professionals/systems/hospital/engagingfamilies/guide.html

Ahlqvist-Björkroth, S., Boukydis, Z., & Lehtonen, L. (2013). *Close collaboration with parents training program: For implementing family centered care culture in neonatal intensive care units*. Turku, Finland: Turku University Hospital.

Al Maghaireh, D. F., Abdullah, K. L., Chan, C. M., Piaw, C. Y., & Al Kawafha, M. M. (2016). Systematic review of qualitative studies exploring parental experiences in the neonatal intensive care unit. *Journal of Clinical Nursing, 25*, 2745–2756. doi:10.1111/jocn.13259

Als, H., & Gilkerson, L. (1997). The role of relationship-based developmentally supportive newborn intensive care in strengthening outcome of preterm infants. *Seminars in Perinatology, 21*, 178–189. doi:10.1016/S0146-0005(97)80062-6

Amin, N. A. L., Tam, W. W. S., & Shorey, S. (2018). Enhancing first-time parents' self-efficacy: A systematic review and meta-analysis of universal parent education interventions' efficacy. *International Journal of Nursing Studies, 82*, 149–162. doi:10.1016/j.ijnurstu.2018.03.021

Ardal, F., Sulman, J., & Fuller-Thomson, E. (2011). Support like a walking stick: Parent-buddy matching for language and culture in the NICU. *Neonatal Network, 30*(2), 89–98. doi:10.1891/0730-0832.30.2.89

Aronson, P. L., Yau, J., Helfaer, M. A., & Morrison, W. (2009). Impact of family presence during pediatric intensive care unit rounds on the family and medical team. *Pediatrics, 124*(4), 1119–1125. doi:10.1542/peds.2009-0369

Axelin, A., Lehtonen, L., Pelander, T., & Salantera, S. (2010). Mothers' different styles of involvement in preterm infant pain care. *Journal of Obstetric, Gynecologic, & Neonatal Nursing, 39*(4), 415–424. doi:10.1111/j.1552-6909.2010.01150.x

Baker, B. J., & McGrath, J. M. (2010). Promoting parenting through single-room care in the NICU. *Newborn and Infant Nursing Reviews, 10*(2), 72–73. doi:10.1053/j.nainr.2010.03.001

Baker, B. J., & McGrath, J. M. (2011). Maternal infant synchrony: An integrated review of the literature. *Neonatal, Paediatric, and Child Health Nursing, 14*(3), 2–13.

Bally, J. M. G., Smith, N. R., Holtslander, L., Duncan, V., Hodgson -Viden, H., Mpofu, C., & Zimmer, M. (2018). A metasynthesis: Uncovering what is known about the experiences of families with children who have life-limiting and life-threatening illnesses. *Journal of Pediatric Nursing, 38*, 88–98. doi:10.1016/j.pedn.2017.11.004

Barnard, R. S., Williams, S. E., Storfer-Isser, A., Rhine, W., Horwitz, S. M., Koopman, C., & Shaw, R. J. (2011). Brief cognitive-behavioral intervention for maternal depression and trauma in the neonatal intensive care unit: A pilot study. *Journal of Traumatic Stress, 24*(2), 230–234. doi:10.1002/jts.20626

Bartlett, D. J., Nijhuis-van der Sanden, M. W. G., Fallang, B., Fanning, J. K., & Doralp, S. (2011). Perceptions of vulnerability and variations in childrearing practices of parents of infants born preterm. *Pediatric Physical Therapy*, *23*, 280–288. doi:10.1097/PEP.0b013e318227cc6b

Baum, N., Weidberg, Z., Osher, Y., & Kohelet, D. (2012). No longer pregnant, not yet a mother: Giving birth prematurely to a very-low-birth-weight baby. *Qualitative Health Research, 22*(5), 595–606. doi:10.1177/1049732311422899

Beck, C. T. (2011). A metaethnography of traumatic childbirth and its aftermath: Amplifying causal looping. *Qualitative Health Research, 21*, 301–311. doi:10.1177/1049732310390698

Bonnier, C. (2008). Evaluation of early stimulation programs for enhancing brain development. *Acta Paediatrica, 97*(7), 853–858. doi:10.1111/j.1651-2227.2008.00834.x

Bos, L. S., Shorey, S., Kulantaipian, T. S., Sng, J. S. P., Tam, W. W. S., & Koh, S. S. L. (2018). Effectiveness of the neonatal discharge program for very low-birth-weight infants on parental efficacy and psychological distress. *Journal of Perinatal and Neonatal Nursing, 32*(4), E11–E21. doi:10.1097/JPN.0000000000000337

Boundy, E. O., Dastjerdi, R., Spiegelman, D., Fawzi, W. W., Missmer, S. A., Lieberman, E., . . . Chan, G. J. (2016). Kangaroo mother care and neonatal outcomes: A meta-analysis. *Pediatrics, 137*(1), e20152238. doi:10.1542/peds.2015–2238

Boykova, M., & Kenner, C. (2010). Partnerships in care: Mothers and fathers. In C. Kenner & J. M. McGrath (Eds.), *Developmental care of newborns and infants: A guide for health professionals* (2nd ed., pp. 145–160). Glenview, IL: National Association of Neonatal Nurses.

Boykova, M., & Kenner, C. (2012). Transition from hospital to home for parents of preterm infants. *Journal of Perinatal and Neonatal Nursing, 26*(1), 81–87. doi:10.1097/JPN.0b013e318243e948

Bracht, M., O'Leary, L., Lee, S. K., & O'Brien, K. (2013). Implementing family-integrated care in the NICU: A parent education and support program. *Advances in Neonatal Care, 13*(2), 115–126. doi:10.1097/ANC.0b013e318285fb5b

Breitenstein, S. M., Gross, D., & Christophersen, R. (2014). Digital delivery methods of parenting training interventions: A systematic review. *Worldviews on Evidence-Based Nursing, 11*(3), 168–176. doi:10.1111/wvn.12040

Brett, J., Staniszewska, S., Newburn, M., Jones, N., & Yaylor, L. (2011). A systematic mapping review of effective interventions for communicating with, supporting and providing information to parents of preterm infants. *BMJ Open, 1*, e000023. doi:10.1136/bmjopen-2010-000023

Brooks, S., Rowley, S., Broadbent, E., & Petrie, K. J. (2012). Illness perception ratings of high-risk newborns by mothers and clinicians: Relationship to illness severity and maternal stress. *Health Psychology, 31*(5), 632–639. doi:10.1037/a0027591

Butt, M., McGrath, J. M., & Samra, H. (2013). An integrative review of parent satisfaction in the NICU. *Journal of Obstetrical, Gynecological and Neonatal Nursing, 42*(1), 106–120. doi:10.1111/1552-6909.12002

Caeymaex, L., Jousselme, C., Vasilescu, C., Danan, C., Falissard, B., Bourrant, M.-M., . . . Speranza, M. (2012). Perceived role in end-of-life decision making in the NICU affects long-term parental grief response. *Archives of Diseases in Child and Fetal Neonatal Edition, 98*, F1–F6. doi:10.1136/archdischild-F2 of F6 2011-301548

Campbell-Yeo, M., Dol, J., Disher, T., Benoit, B., Chambers, C., Sheffield, K., . . . Caddell, K. (2017). The power of a parent's touch: Evaluation of reach and impact of a targeted evidence-based YouTube video. *Journal of Perinatal and Neonatal Nursing, 31*(4), 341–349. doi:10.1097/JPN.0000000000000263

Carroll, C., Carroll, C., Goloff, N., & Pitt, M. B. (2018). When bad news isn't necessarily bad: Recognizing provider bias when sharing unexpected news. *Pediatrics, 142*(1), e201–e204. doi:10.1542/peds.2018-0503

Casio, C. J., Moore, D., & McGlone, F. (2018). Social touch and human development. *Developmental Cognitive Neuroscience, 35*, 5–11. doi:10.1016/j.dcn.2018.04.009

Celenza, J. F., Zayack, D., Buus-Frank, M. E., & Horbar, J. D. (2017). Family involvement in quality improvement: From bedside advocate to system advisor. *Clinics in Perinatology, 44*, 553–566. doi:10.1016/j.clp.2017.05.008

Cho, E.-S., Kim, S.-J., Kwon, M. S., Cho, H., Kim, E. H., Jun, E. M., & Lee, S. (2016). The effects of kangaroo care in the neonatal intensive care unit on the physiological functions of preterm infants, maternal-infant attachment, and maternal stress. *Journal of Pediatric Nursing, 31*, 430–438. doi:10.1016/j.pedn.2016.02.007

Cisneros Moore, K. A., Coker, K., DuBuisson, A. B., Swett, B., Edwards, W. H. (2003). Implementing potentially better practices for improving family-centered care in neonatal intensive care units: successes and challenges. *Pediatrics*, *111*(4 Pt 2), e450–60. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/12671165

Cleveland, L. M. (2008). Parenting in the neonatal intensive care unit. *Journal of Obstetric, Gynecologic, & Neonatal Nursing, 37*(6), 666–691. doi:10.1111/j.1552-6909.2008.00288.x

Coughlin, M. B., & Sethares, K. A. (2017). Chronic sorrow in parents of children with a chronic illness or disability: An integrative literature review. *Journal of Pediatric Nursing, 37*, 108–116. doi:10.1016/j.pedn.2017.06.011

Coulter, A., & Ellins, J. (2007). Effectiveness of strategies for informing, educating, and involving patients. *British Medical Journal*, *335*, 24–27.

Craig, J. W., Glick, C., Phillips, R., Hall, S. L., Smith, J., & Browne, J. (2015). Recommendations for involving the family in developmental care of the NICU baby. *Journal of Perinatology, 35*(Suppl.), S5–S8. doi:10.1038/jp.2015.142

Curley, M. A., Hunsberger, M., & Harris, S. K. (2013). Psychometric evaluation of the family-centered care scale for pediatric acute care nursing. *Nursing Research, 62*(3), 60–68. doi:10.1097/NNR.0b013e318286d64b

Currie, E. R., Christian, B. J., Hinds, P. S., Perna, S. J., Robinson, C., Day, S., & Meneses, K. (2016). Parents' perspectives of neonatal intensive care at the end-of life. *Journal of Pediatric Nursing, 31*, 478–489. doi:10.1016/j.pedn.2016.03.023

Curtis, K., Foster, K., Mitchell, R., & Van, C. (2016). Models of care delivery for families of critically ill children: An integrative review of international literature. *Journal of Pediatric Nursing, 31*, 330–341. doi:10.1016/j.pedn.2015.11.009

D'Agata, A., Coughlin, M., & Sanders, M. (2018). Clinician perceptions of the NICU infant experience: Is the NICU hospitalization traumatic? *American Journal of Perinatology, 35*(12), 1159–1167. doi:10.1055/s-0038-1641747

D'Agata, A., & McGrath, J. (2016). A framework of complex adaptive systems: Parents as partners in the NICU. *Advances in Nursing Science, 39*(3) 244–256. doi:10.1097/ANS.0000000000000127

D'Agata, A., Sanders, M., Grasso, D. J., Young E., Cong, X., & McGrath, J. M. (2017). Unpacking the burden of care for infants in the NICU. *Infant Mental Health Journal, 38*(2), 306–317. doi:10.1002/imhj.21636

D'Agata, A., Young, E., Cong, X., Grasso, D. J., & McGrath, J. M. (2016). Infant medical trauma in the neonatal intensive care unit (IMTN). *Advances in Neonatal Care*, *16*(4), 289–297. doi:10.1097/ANC.0000000000000309

DeMauro, S. B., Cairnie, J., D'Ilario, J., Kirpalani, H., & Schmidt, B. (2014). Honesty, trust, and respect during consent discussions in neonatal clinical trials. *Pediatrics, 134*, e1–e5. doi:10.1542/peds.2013-3720

Domanico, R., Davis, D. K., Coleman, F., & Davis, B. O. (2010). Documenting the NICU design dilemma: Parent and staff perceptions of open ward versus single family room units. *Journal of Perinatology, 30*, 343–351. doi:10.1038/jp.2009.195

Drenkard, K. (2014). Patient engagement. *Journal of Nursing Administration, 44*(1), 3–4. doi:10.1097/NNA.0000000000000022

Dykes, F., Thompson, G., Gardner, C., Moran, V. H., & Flacking, R. (2016). Perceptions of European medical staff on the facilitators and barriers to physical closeness between parents and infants in neonatal units. *Acta Paediatrica, 105*, 1039–1046. doi:10.1111/apa.13417

Ekeus, C., Lindström, K., Lindblad, F., Rasmussen, F., & Hjern, A. (2010). Preterm birth, social disadvantage, and cognitive competence in Swedish 18- to 19-year-old men. *Pediatrics, 125*, e67–e73. doi:10.1542/peds.2008-3329

Epstein, E. G., Miles, A., Rovnak, V., & Baernholdt, M. (2013). Parents' perceptions of continuity of care in the neonatal intensive care unit: Pilot testing an instrument and implications for the nurse-parent relationship. *Journal of Perinatal and Neonatal Nursing, 27*(2), 168–175. doi:10.1097/JPN.0b013e31828eafbb

Feeley, N., Genest, C., Niela-Vilén, H., Charbonneau, L., & Axelin, A. (2016). Parents and nurses balancing parent–infant closeness and separation: A qualitative study of NICU nurses' perceptions. *BMC Pediatrics, 16*, 134, 1–13. doi:10.1186/s12887-016-0663-1

Fidler, H., & McGrath, J. M. (2009). Neonatal transport: The family perspective. *Newborn and Infant Nursing Reviews, 9*(4), 187–190. doi:10.1053/j.nainr.2009.09.010

Flacking, R., Thomson, G., & Axelin, A. (2016). Pathways to emotional closeness in neonatal units—A cross-national qualitative study. *BMC Pregnancy and Childbirth, 16*, 170. doi:10.1186/s12884-016-0955-3

Foster, M., Whitehead, L., Arabiat, D., & Frost, L. (2018). Parents' and staff perceptions of parental needs during a child's hospital admission: An Australian study. *Journal of Pediatric Nursing, 53*, 1167–1175. doi:10.1016/j.pedn.2018.06.013

Franck, L. S., & Axelin, A. (2013). Differences in parents', nurses' and physicians' views of NICU parent support. *Acta Paediatrica, 102*, 590–596. doi:10.1111/apa.12227

Frisman, G. H., Eriksson, C., Pernehed, S., & Morelius, E. (2012). The experience of becoming a grandmother to a premature infant—A balancing act, influenced by ambivalent feelings. *Journal of Clinical Nursing, 21*, 21–22. doi:10.1111/j.1365-2702.2012.04204.x

Galarza-Winton, M. E., Dicky, T., O'Leary, L., Lee, S. K., & O'Brien. (2013). Implementing family-integrated care in the NICU. *Advances in Neonatal Care, 13*(5), 335–340. doi:10.1097/ANC.0b013e3182a14cde

Garfield, C. F., Simon, C. D., Rutsohn, J., & Lee, Y. S. (2018). Stress from the neonatal intensive care unit to home. *Journal of Perinatal and Neonatal Nursing, 32*(3), 257–265. doi:10.1097/JPN.0000000000000296

Gasparini, R., Hudson, J., Champagne, M., Fuchs, M. A., & Stephany, A. (2015). Policy to practice: Increased family presence and the impact on patient- and family-centered care adoption. *Journal of Nursing Administration, 45*(1), 28–34. doi:10.1097/NNA.0000000000000152

Giambra, B. K., Broome, M. E., Sabourin, T., Buelow, J., & Stiffler, D. (2017). Integration of parent and nursing perspectives of communication to plan of care for technology dependent children: The theory of shared communication. *Journal of Pediatric Nursing, 34*, 29–35. doi:10.1016/j.pedn.2017.01.014

Gooding, J. S., Cooper, L. G., Blaine, A. I., Franck, L. S., Howse, J. L., & Berns, S. D. (2011). Family support and family-centered care in the neonatal intensive care unit: Origins, advances, impact. *Seminars in Perinatology, 35*, 20–28. doi:10.1053/j.semperi.2010.10.004

Gray, P. H., Edwards, D. M., O'Callaghan, M. J., & Cuskelly, M. (2012). Parenting stress in mother of preterm infants during early infancy. *Early Human Development, 88*(1), 45–49. doi:10.1016/j.earlhumdev.2011.06.014

Green, J., Darbyshire, P., Adams, A., & Jackson, D. (2015). Desperately seeking parenthood: Neonatal nurses reflect on parental anguish. *Journal of Clinical Nursing, 24*, 1885–1894. doi:10.1111/jocn.12811

Greene, J., & Hibbard, J. H. (2012). Why does patient activation matter? An examination of the relationships between patient activation and health-related outcomes. *Journal of General Internal Medicine, 27*, 520–526. doi:10.1007/s11606-011-1931-2

Greisen, G., Mirante, N., Haumount, D., Pierrat, V., Pallás-Alonso, C. R., Warren, I., . . . Cuttini, M. (2009). Parents, siblings and grandparents in the neonatal intensive care unit: A survey of policies in eight European countries. *Acta Pædiatrica, 98*, 1744–1750. doi:10.1111/j.1651-2227.2009.01439.x

Griffin, T. (2013). A family-centered visitation policy on the neonatal intensive care unit that welcomes parents as partners. *Journal of Perinatal and Neonatal Nursing, 27*(2), 160–165. doi:10.1097/JPN.0b013e3182907f26

Grzyb, M. J., Coo, H., Ruland, L., & Dow, K. (2014). Views of parent and health-care providers regarding parental presence during bedside rounds in a neonatal intensive care unit. *Journal of Perinatology, 34*, 143–148. doi:10.1038/jp.2013.144

Hägi-Pedersen, M., Norlyk, A., Dessau, R., Stanchev, H., & Kronborg, H. (2017). Multicentre randomised study of the effect and experience of an early in home programme (PreHomeCare) for preterm infants using video consultation and smartphone applications compared with in hospital consultations: Protocol of the PreHomeCare study. *BMJ Open, 7*, e013024. doi:10.1136/bmjopen-2016-013024

Hall, S. L., Cross, J., Selix, N. W., Patterson, C., Segre, L., Chuffo-Siewert, R., . . . Martin, M. L. (2015). Recommendations for enhancing psychosocial support of NICU parents through staff education and support. *Journal of Perinatology, 35*(Suppl.), S29–S36. doi:10.1038/jp.2015.147

Hall, S. L., Hynan, M. T., Phillips, R., Patterson, C., Segre, L., Chuffo-Siewert, R., . . . Martin, M. L. (2017). The neonatal intensive parenting unit: An introduction. *Journal of Perinatology, 37*, 1259–1264. doi:10.1038/jp.2017.108

Hall, S. L., Ryan, D. J., Beatty, J., & Grubb, L. (2015). Recommendations for peer-to-peer support for NICU parents. *Journal of Perinatology, 35*(Suppl.), S9–S13. doi:10.1038/jp.2015.143

Hall-Johnson, S. (1986). *Nursing assessment and strategies for the family at risk* (2nd ed.). Philadelphia, PA: Lippincott Williams & Wilkins.

Hardy, W., & McGrath, J. M. (2008). Supporting information-seeking behaviors of families in the 21st century. *Newborn and Infant Nursing Reviews, 8*(3), 118–119. doi:10.1053/j.nainr.2008.06.013

Heidari, H., Hasanpour, M., Fooladi, M., & Awat, F. (2015). Construction of a questionnaire to assess parental stress in neonatal intensive care unit. *Iranian Journal of Neonatology, 6*(3), 12–16. doi:10.22038/IJN.2015.4889

Herd, M., Whittingham, K., Sanders, M., Colditz, P., & Boyd, R. (2014). Efficacy of preventive parenting interventions for parents of preterm infants on later child behavior: A systematic review and meta-analysis. *Infant Mental Health Journal, 35*(6), 630–641. doi:10.1002/imhj.21480

Hibbard, J. H., & Greene, J. (2013). What the evidence shows about patient activation: Better health outcomes and care experience; fewer data on costs. *Health Affairs,* 32(2), 207–214. doi:10.1377/hlthaff.2012.1061

Hill, C., Knafl, K. A., & Santacroce, S. J. (2018). Family-centered care from the perspective of parents of children cared for in a pediatric intensive care unit: An integrative review. *Journal of Pediatric Nursing, 41*, 22–33. doi:10.1016/j.pedn.2017.11.007

Hodnett, E. D., Gates, S., Hofmeyr, G. J., Sakala, C., & Weston, J. (2011). Continuous support for women during childbirth. *Cochrane Database of Systematic Reviews*, (2), CD003766. doi:10.1002/14651858.CD003766.pub3

Hopwood, N., Clerke, T., & Nguyen, A. (2017). A pedagogical framework for facilitating parents' learning in nurse-parent partnerships. *Nursing Inquiry, 25*(2), e12220. doi:10.1111/nin.12220

Howland, L. C., Pickler, R. H., McCain, N. L., Glaser, D., & Lewis, M. (2011). Exploring biobehavioral outcomes in mothers of preterm infants. *American Journal of Maternal Child Nursing, 36*(2), 91–97. doi:10.1097/NMC.0b013e318205587e

Hynan, M. T., Steinberg, Z., Baker, L., Cicco, R., Geller, P. A., Lassen, S., . . . Stuebe, A. (2015). Recommendations for mental health professionals in the NICU. *Journal of Perinatology, 35*(Suppl.), S14–S18. doi:10.1038/jp.2015.144

Ichijima, E., Kirk, R., & Hornblow, A. (2011). Parental support in neonatal intensive care units: A cross-cultural comparison between New Zealand and Japan. *Journal of Pediatric Nursing, 26*, 206–215. doi:10.1016/j.pedn.2009.10.003

Ingram, J., Redshaw, M., Manns, S., Beasant, L., Johnson, D., Fleming, P., & Pontin, D. (2017). "Giving us hope": Parent and neonatal staff views and expectations of a planned family centered discharge process (Train-to-Home). *Health Expectations, 20*, 751–759. doi:10.1111/hex.12514

Institute for Patient- and Family-Centered Care. (2010a). *Changing hospital "visiting" policies and practices: Supporting family presence and participation: Executive statement*. Bethesda, MD: Author. Retrieved from http://www.ipfcc.org/resources/visiting.pdf

Institute for Patient- and Family-Centered Care. (2010b). *HIPAA—Providing the opportunities for collaboration*. Bethesda, MD: Author. Retrieved from http://www.ipfcc.org/resources/hipaa.pdf

Institute for Patient- and Family-Centered Care. (2013a). *HIPAA privacy and security rules and Joint Commission standards are NOT BARRIERS to advancing patient- and family-centered care and building partnerships with patients and families; fact sheet*. Bethesda, MD: Author. Retrieved from http://www.ipfcc.org/bestpractices/HIPAA-Factsheet.pdf

Institute for Patient- and Family-Centered Care. (2013b). *Partnering with patients and families to enhance safety and quality: A mini toolkit*. Bethesda, MD: Author. Retrieved from http://www.ihi.org/education/conferences/APACForum2012/Documents/I1_Toolkit.pdf

Institute for Patient- and Family-Centered Care. (2017). *Advancing the practice of patient- and family-centered care in hospitals: How to get started*. Bethesda, MD: Author. Retrieved from http://www.ipfcc.org/resources/getting_started.pdf

Institute for Patient- and Family-Centered Care. (2018). *Diverse voices matter: Improving diversity in patient and family advisory councils*. Bethesda, MD: Author. Retrieved from http://www.ipfcc.org/resources/Diverse-Voices-Matter.pdf

Jackson, D. B., Newsome, J., & Beaver, K. M. (2016). Does early paternal involvement predict offspring developmental diagnoses? *Early Human Development, 103*, 9–16. doi:10.1016/j.earlhumdev.2016.07.001

Johnson, B., Abraham, M., Conway, J., Simmons, L., Edgman-Levitan, S., Sodomka, P., . . . Ford, D. (2008). *Partnering with patients and families to design a patient- and family-centered health care system: Recommendations and Promising Practices*. Bethesda, MD: Institute for Family-Centered Care and Institute for Healthcare Improvement.

Jones, L., Peters, K., Rowe, J., & Sheeran, N. (2016). The influence of neonatal nursery design on mothers' interactions in the nursery. *Journal of Pediatric Nursing, 31*, e301–312. doi:10.1016/j.pedn.2016.05.005

Kaakinen, J., Gedaly-Duff, V., Hanson, S., & Coehlo, D. (Eds.). (2009). *Family health care nursing: Theory, practice and research* (4th ed.). Philadelphia, PA: F. A. Davis.

Kamphorst, K., Brouwer, A. J., Poslawsky, I. E., Ketelaar, M., Ockhuisen, H., & van den Hoogen, A. (2018). Parental presence and activities in a Dutch neonatal intensive care unit. *Journal of Perinatal and Neonatal Nursing, 32*(3), E3–E10. doi:10.1097/JPN.0000000000000354

Karatzias, T., Chouliara, Z., Maxton, F., Freer, Y., & Power, K. (2007). Post-traumatic symptomatology in parents with premature infants: A systematic review of the literature. *Journal of Prenatal and Perinatal Psychology and Health, 21*(3), 249–260. Retrieved from https://birthpsychology.com/journal/article/post-traumatic-symptomatology-parents-premature-infants-systematic-review-literature

Kellie, S. M., Makvandi, M., & Muller, M. L. (2011). Management and outcome of a varicella exposure in a neonatal intensive care unit: Lessons for the vaccine era. *American Journal of Infection Control, 39*(10), 844–848. doi:10.1016/j.ajic.2011.02.006

Kersten-Alvarez, L. E., Hossman, C. M. H., Riksen-Walraven, J. M., Van Doesum, K. T. M., & Hoefnagels, C. (2011). Which preventive intervention effectively enhances depressed mother's sensitivity? A meta-analysis. *Infant Mental Health Journal, 32*(3), 362–376. doi:10.1002/imhj.20301

Kim, H. N. (2018). Social support provision: Perspective of fathers with preterm infants. *Journal of Pediatric Nursing, 39*, 44–48. doi:10.1016/j.pedn.2018.01.017

Kjellsdotter, A., Lantz, B., & Ottosson, C. (2018). Healthcare professionals' views on parental participation in the neonatal intensive care units. *Journal of Pediatric Nursing, 41*, 3–8. doi:10.1016/j.pedn.2017.09.008

Klegerg, A., Hellstrom-Westas, L., & Widstrom, A. M. (2007). Mother's perception of Newborn Individualized Developmental Care and Assessment Program (NIDCAP) as compared to conventional care. *Early Human Development, 83*, 403–411. doi:10.1016/j.earlhumdev.2006.05.024

Latour, J. M., Hazelzet, J. A., Duivenvoorden, H. J., & van Goudoever, J. B. (2010). Perceptions of parents, nurses, and physicians on neonatal intensive care practices. *Journal of Pediatrics, 157*, 215–220. doi:10.1016/j.jpeds.2010.02.009

Lee, L. A., Carter, M., Stevenson, S. B., & Harrison, H. A. (2014). Improving family-centered care practices in the NICU. *Neonatal Network, 33*(3), 125–132. doi:10.1891/0730-0832.33.3.125

Lindner, S. L., & McGrath, J. M. (2012). Family-centered care in the delivery room environment. *Newborn and Infant Nursing Reviews, 12*(2), 70–72. doi:10.1053/j.nainr.2012.03.004

Lipson, J. G., & Dibble, S. L. (Eds.). (2005). *Culture and clinical care*. San Francisco, CA: USCF Nursing Press.

Liu, C.-H., Chao, Y.-H., Haung, C.-M., Wei, F.-C., & Chien, L.-Y. (2010). Effectiveness of applying empowerment strategies when establishing a support group for parent of preterm infants. *Journal of Clinical Nursing, 19*, 1729–1737. doi:10.1111/j.1365-2702.2009.03082.x

Lopez, G. L., Anderson, K. H., & Feutchinger, J. (2012). Transition of premature infants from hospital to home life. *Neonatal Network, 31*(4), 207–214. doi:10.1891/0730-0832.31.4.207

Ludington-Hoe, S. (2011). Evidence-based review of physiologic effects of kangaroo care. *Current Womens Health Reviews, 2011*, 243–253. doi:10.2174/157340411796355162

Macdonell, K., Christie, K., Robson, K., Pytlik, K., Lee, S., & O'Brien, K. (2013). Implementing family-integrated care in the NICU: Engaging veteran parents in program design and delivery. *Advances in Neonatal Care, 13*(4), 262–269. doi:10.1097/ANC.0b013e31829d8319

Makris, N., Vittner, D., Samra, H., & McGrath, J. (2019). Further understanding of the PREEMI as a measure of parent engagement in the NICU. *Applied Nursing Research, 47*, 24–28. doi:10.1016/j.apnr.2019.03.007

Mangureten, J., Scott, S. H., Guzetta, C. E., Clark, A. P., Vinso, L., Sperry, J. . . . Voelmeck, W. (2005). Effects of family presence during resuscitation and invasive procedures in a pediatric emergency department. *Journal of Emergency Nursing, 32*(3), 225–233. doi:10.1016/j.jen.2006.02.012

Matsuda, Y., & McGrath, J. M. (2011). Working in a global village: Cultural competency and collaboration through interpreters. *Newborn and Infant Nursing Reviews, 11*(3), 102–104. doi:10.1053/j.nainr.2011.07.001

McAnulty, G., Duffy, F., Kosta, S., Weisenfeld, N., Warfield, S., Butler, S., . . . Als, H. (2013). School age effects of the newborn individualized developmental care and assessment program for preterm infants with intrauterine growth restriction: Preliminary findings. *BMC Pediatrics, 13*, 25. doi:10.1186/1471-2431-13-25

McCann, D., Young, J., Watson, K., Ware, R. S., Pitcher, A., Bundy, R., & Tutur, D. G. (2008). Effectiveness of a tool to improve role negotiation and communication between parents and nurses. *Paediatric Nursing, 20*(5), 15–19.

McCormick, M. C., Escobar, G. J., Zgeng, Z., & Richardson, D. K. (2008). Factors influencing parental satisfaction with neonatal intensive care among the families of moderately premature infants. *Pediatrics, 121*, 1111–1118. doi:10.1542/peds.2007-1700

McGrath, J. M. (2007a). Family caregiving: Synchrony with infant caregiving? *Newborn and Infant Nursing Reviews, 7*(1), 1–2. doi:10.1053/j.nainr.2006.12.003

McGrath, J. M. (2007b). "Will my baby be normal?" Helping families make informed decisions related to neonatal surgery. *Journal of Perinatal and Neonatal Nursing, 21*(1), 4–5. doi:10.1097/00005237-200701000-00003

McGrath, J. M. (2008). Maturation of infant learning in the NICU. *Journal of Perinatal and Neonatal Nursing, 22*(4), 257–258. doi:10.1097/01.JPN.0000341353.99703.7c

McGrath, J. M. (2011). Strategies for increasing parent presence in the NICU. *Journal of Perinatal and Neonatal Nursing, 25*(4), 305–306. doi:10.1097/JPN.0b013e318235e584

McGrath, J. M. (2012). Strategies to support the transition to home. *Journal of Perinatal and Neonatal Nursing, 26*(1), 8–9. doi:10.1097/JPN.0b013e3182437255

McGrath, J. M. (2013). Important reminder: All neonatal caregivers are Brain Shapers. *Journal of Perinatal and Neonatal Nursing, 27*(3), 199–200. doi:10.1097/JPN.0b013e31829ea0b5

McGrath, J. M., Cone, S., & Samra, H. (2011). Neuroprotection in the preterm infant: Further understanding of the short and long term implications for brain development. *Newborn and Infant Nursing Reviews, 11*(3), 109–112. doi:10.1053/j.nainr.2011.07.002

McGrath, J. M., & Hardy, W. (2008). Communication: An essential component of quality care. *Newborn and Infant Nursing Reviews, 8*(2), 64–66. doi:10.1053/j.nainr.2008.03.005

McGrath, J. M., Samra, H., & Kenner, C. (2011). Family centered developmental care practices and research: What will the next century bring? *Journal of Perinatal and Neonatal Nursing, 25*(2), 165–170. doi:10.1097/JPN.0b013e31821a6706

McGrath, J. M., Samra, H., Zukowsky, K., & Baker, B. (2010). Parenting after infertility: Issues for families and infants. *The American Journal of Maternal Child Nursing, 35*(3), 157–164. doi:10.1097/NMC.0b013e3181d7657d

Meiers, S., Tomlinson, P., & Peden-McAlpine, C. (2007). Development of the family nurse caring belief scale (FNCBS). *Journal of Family Nursing, 13*(4), 484–502. doi:10.1177/1074840707310734

Melnyk, B. M., & Fineout-Overholt, E. (Eds.). (2010). *Evidence-based practice in nursing and health care: A guide to best practice* (2nd ed.). Philadelphia, PA: Lippincott Williams & Wilkins.

Menghini, K. G. (2005). Designing and evaluating parent educational materials. *Advances in Neonatal Care, 5*(5), 273–283. doi:10.1016/j.adnc.2005.07.003

Milette, I., Martel, M. J., Ribeiro da Silva, M., & Coughlin, M. (2017a). Guidelines for the institutional implementation of developmental neuroprotective care in the NICU. Part A: Background and rationale. A joint position statement from the CANN, CAPWHN, COINN, NANN. *Canadian Journal of Nursing Research, 49*, 46–62. doi:10.1177/0844562117706882

Milette, I., Martel, M. J., Ribeiro da Silva, M., & Coughlin, M. (2017b). Guidelines for the institutional implementation of developmental neuroprotective care in the NICU. Part B: Recommendations and justification. A joint position statement from the CANN, CAPWHN, COINN & NANN. *Canadian Journal of Nursing Research, 49*, 63–74. doi:10.1177/0844562117708126

Miyagishima, S., Himuro, N., Kozuka, N., Mori, M., & Tsutsumi, H. (2017). Family-centered care for preterm infants: Parent and physical therapist perceptions. *Pediatrics International, 59*, 698–703. doi:10.1111/ped.13266

Montirosso, R., Del Prete, A., Bellù, R., Tronick, E., Borgatti, R., & Neonatal Adequate Care for Quality of Life (NEO-ACQUA) Study Group. (2012). Level of NICU quality of developmental care and neurobehavioral performance in very preterm infants. *Pediatrics, 129*, e1129–e1137. doi:10.1542/peds.2011-0813

Moradi, S., Arshdi-Bostanabad, M., Seyedrasooli, A., Tapak, L., & Valizadeh, S. (2018). The effect of empowerment program on maternal discharge preparation and neonatal length of hospital stay: A randomized controlled trial. *Iran Journal of Nursing and Midwifery Research, 23*(3), 172–177. doi:10.4103/ijnmr.IJNMR_110_17

Morey, J. A., & Gregory, K. (2012). Nurse-led education mitigates maternal stress and enhances knowledge in the NICU. *American Journal of Maternal Child Health, 37*(3), 182–191. doi:10.1097/NMC.0b013e31824b4549

Mori, R., Khanna, R., Pledge, D., & Nakayama, T. (2010). Meta-analysis of physiologic effects of skin to skin contact for newborns and mothers. *Pediatrics International, 52*, 161–170. doi:10.1111/j.1442-200x.2009.02909.x

Morrison, A., & Gullon-Rivera, A. L. (2017). Supporting siblings of neonatal intensive care unit patients: A NICU social story™ as an innovative approach. *Journal of Pediatric Nursing, 33*, 91–93. doi:10.1016/j.pedn.2016.12.002

Mortessen, J. A., & Mastergeorge, A. M. (2014). A meta-analytic review of relationship-based interventions for low-income families with infants and toddlers: Facilitating supportive parent-child interactions. *Infant Mental Health Journal, 35*(4), 336–353. doi:10.1002/imhj.21451

Mosqueda, R., Castilla, Y., Perapoch, J., da la Cruz, J., Lopez-Maestro, M., & Pallas, C. (2013). Staff perceptions on newborn individualized developmental care and assessment program (NIDCAP) during its implementation in two Spanish neonatal units. *Early Human Development, 89*(1), 27–33. doi:10.1016/j.earlhumdev.2010.07.013

Mundy, C. A. (2010). Families in critical care; assessment of family needs in neonatal care units. *American Journal of Critical Care, 19*, 156–163. doi:10.4037/ajcc2010130

Neel, M. L. M., Stark, A. R., & Maitre, N. L. (2018). Parenting style impacts cognitive and behavioural outcomes of former preterm infants: A systematic review. *Child Care Health and Development, 44*, 507–515. doi:10.1111/cch.12561

Neu, M., & Robinson, J. A. (2010). Maternal holding of preterm infant during the early weeks after birth and dyad interaction at six months. *Journal of Obstetric, Gynecologic, & Neonatal Nursing, 39*(4), 401–414. doi:10.1111/j.1552-6909.2010.01152.x

Newnam, K. M., & McGrath, J. M. (2010). Families and the sepsis work-up: Considering their fears. *Newborn and Infant Nursing Reviews, 10*(4), 160–162. doi:10.1053/j.nainr2010.09.004

Niela-Vilén, H., Feeley, N., & Axelin, A. (2017). Hospital routines promote parent–infant closeness and cause separation in the birthing

unit in the first 2 hours after birth: A pilot study. *Birth, 44*, 167–172. doi:10.1111/birt.12279

Nightingale, R., Wirz, L., Cook, W., & Swallow, V. (2017). Collaborating with parents of children with chronic conditions and professionals to design, develop and pre-pilot PLAnT (the Parent Learning Needs and Preferences Assessment Tool). *Journal of Pediatric Nursing, 35*, 90–97. doi:10.1016/j.pedn.2017.03.008

Ninomura, P., Rousseau, C., & Bartley, J. (2006). Updated guidelines for design and construction of hospital and health care facilities. *ASHRAE Journal (American Society of Heating, Refrigerating and Air-Conditioning Engineers, Inc.)*, *48*(6), H33–H37.

Nordheim, T., Anderzen-Carlsson, A., & Nakstad, B. (2018). A qualitative study of the experiences of Norwegian parents of very low birthweight infants enrolled in a randomized nutritional trial. *Journal of Pediatric Nursing, 43*, e66–e74. doi:10.1016/j.pedn.2018.07.008

Nordheim, T., Rustøen, T., Solevåg, A. L., Småstuen, M. C., & Nakstad, B. (2018). Hope in parents of very-low birth weight infants and its association with parenting stress and quality of life. *Journal of Pediatric Nursing, 38*, e53–e58. doi:10.1016/j.pedn.2017.10.006

O'Brien, K., Bracht, M., Macdonell, K., McBride, T., Robson, K., O'Leary, L., . . . Lee, S. K. (2013). A pilot cohort analytic study of family integrated care in a Canadian neonatal intensive care unit. *BMC Pregnancy and Childbirth, 13*(Suppl. 1), S12. doi:10.1186/1471-2393-13-S1-S12

O'Brien, K., Bracht, M., Robson, K., Ye, X., Mirea, L., Cruz, M., . . . Lee, S. (2015). Evaluation of the family integrated care model of neonatal intensive care: A cluster randomized controlled trial in Canada and Australia. *BMC Pediatrics, 15*, 210. doi:10.1186/s12887-015-0527-0

Olsson, E., Eriksson, M., & Anderzen-Carlsson, A. (2017). Skin-to-skin contact facilitates more equal parenthood: A qualitative study from father' perspective. *Journal of Pediatric Nursing, 34*, e2–e9. doi:10.1016/j.pedn.2017.03.004

Palomaa, A-K., Korhonen, A., & Pölkki, T. (2016). Factors influencing parental participation in neonatal pain alleviation. *Journal of Pediatric Nursing, 31*, 519–527. doi:10.1016/j.pedn.2016.05.004

Pelentsov, L. J., Fielder, A. L., & Esterman, A. J. (2016). The supportive care needs of parents with a child with a rare disease: A qualitative descriptive study. *Journal of Pediatric Nursing, 31*, e207–e218. doi:10.1016/j.pedn.2015.10.022

Peyrovi, H., Mosayebi, Z., Mohammad-Doost, F., Chehrzad, M.-M., & Mehran, A. (2015). The effect of empowerment program on "perceived readiness for discharge" of mothers of premature infants. *The Journal of Maternal–Fetal and Neonatal Medicine, 29*(5), 752–757. doi:10.3109/14767058.2015.1017461

Pichler-Stachl, E., Pichler, G., Gramm, S., Zotter, H., Mueller, W., & Urlesberger, B. (2011). Prematurity: Influence on mother's locus of control. *Wien Klin Wochenschr: The Central European Journal of Medicine, 123*, 455–457. doi:10.1007/s00508-011-1601-8

Pineda, R. G., Stransky, K. E., Rogers, C., Duncan, M. H., Smith, G. C., Neil, J., & Inder, T. (2012). The single-patient room in the NICU: Maternal and family effects. *Journal of Perinatology, 32*, 545–551. doi:10.1038/jp.2011.144

Poehlmann, J., Miller Schwichtenberg, A. J., Bolt, D., Dilworth-Bart, J. (2009). Predictors of Depressive Symptom Trajectories in Mothers of Infants Born Preterm or Low Birthweight. *Journal of Family Psychology*, *23*(5), 690–704. doi:10.1037/a0016117

Provenzi, L., Barello, S., & Graffigna, G. (2015). Caregiver engagement in the neonatal intensive care unit. Parental needs, engagement milestones, and action priorities for neonatal healthcare of preterm infants. In G. Graffigna, S. Barello, & S. Triberti (Eds.), *Patient engagement: A consumer-centered model to innovate healthcare* (pp. 94–107). Berlin, Germany: Creative Commons: University of Barcelona. doi:10.1515/9783110452440-009

Raines, D. A., & Brustad, J. (2012). Parent's confidence as a caregiver. *Advances in Neonatal Care, 12*(3), 183–188. doi:10.1097/ANC.0b013e318256efd5

Raiskila, S., Axelin, A., Toome, L., Caballero, S., Tandberg, B. S., Montirosso, R., . . . Lehtonen, L. (2017). Parent's presence and parent–infant closeness in 11 neonatal units in six European countries vary between and within the countries. *Acta Pædiatrica, 106*, 878–888. doi:10.1111/apa.13798

Reid, T. (2007). Perceptions of parent-staff communication in neonatal intensive care: The development of a rating scale. *Journal of Neonatal Nursing, 13*, 24–35. doi:10.1016/j.jnn.2006.11.014

Reis, M. D., Rempel, G. R., Scott, S. D., Brady-Fryer, B. A., & van Aerde, J. (2010). Developing nurse/patient relationships in the NICU through negotiated partnerships. *Journal of Obstetric, Gynecologic, & Neonatal Nursing, 39*(6), 675–683. doi:10.1111/j.1552-6909.2010.01189.x

Rogers, C. E., Kidokoro, H., Wallendorf, M., & Inder, T. E. (2013). Identifying mothers of very preterm infants at-risk for postpartum depression and anxiety before discharge. *Journal of Perinatology, 33*(3), 171–176. doi:10.1038/jp.2012.75

Roscigno, C. I., Savage, T. A., Kavanaugh, K., Moro, T. T., Kirkatrick, S. J., Strassner, H. T., . . . Kimura, R. E. (2012). Divergent views of hope influencing communications between parents and hospital providers. *Qualitative Health Research, 22*(9), 1232–1246. doi:10.1177/1049732312449210

Samra, H. A., & McGrath, J. M. (2009). Infant vulnerability and parent overprotection: Recommendations for health professionals. *Newborn and Infant Nursing Reviews, 9*(3), 136–138. doi:10.1053/j.nainr.2009.07.004

Samra, H. A., McGrath, J., Fischer, S., Schumacher, B., Dutcher, J., & Hansen, J. (2015). NICU parent risk evaluation and engagement model instrument (PREEMI) for neonates in intensive care units. *Journal of Obstetric, Gynecologic & Neonatal Nursing, 44*, 114–126. doi:10.1111/1552-6909.12535

Samra, H. A., McGrath, J. M., Wehbe, M., & Clapper, J. (2012). Epigenetics and family centered developmental care of the preterm infant. *Advances in Neonatal Care, 12*(5S), s2–s9. doi:10.1097/ANC.0b013e318265b4bd

Samra, H. A., McGrath, J. M., Wey, H., Schumacher, B., Fischer, S., & Jorgenson, B. (2013). The influence of geographic isolation on late preterm infant and mother outcomes. *Advances in Neonatal Care, 13*(3), 205–215. doi:10.1097/ANC.0b013e318285fd58

Sanders, M. R., & Hall, S. L. (2017). Trauma-informed care in the newborn intensive care unit: Promoting safety, security, and connectedness. *Journal of Perinatology, 38*, 3–10. doi:10.1038/jp.2017.124

Santos, H., Yang, Q., Docherty, S. L., White-Traut, R., & Holditch-Davis, D. (2016). Relationship of maternal psychological distress classes to later mother–infant interaction, home environment, and infant development in preterm infants. *Research in Nursing & Health, 39*, 175–186. doi:10.1002/nur.21719

Shah, P. E., Clements, M., & Poehlmann, J. (2011). Maternal resolution of grief after preterm birth: Implications for infant attachment security. *Pediatrics, 127*(2), 284–292. doi:10.1542/peds.2010-1080

Shieh, S.-J., Chen, H.-L., Liu, F.-C., Liou, C.-C., Lin, Y.-i-H., Teng, H.-I., & Wang, R.-H. (2010). The effectiveness of structured discharge education on maternal confidence, caring knowledge and growth of premature newborns. *Journal of Clinical Nursing, 19*, 3307–3313. doi:10.1111/j.1365-2702.2010.03382.x

Stefana, A., & Lavelli, M. (2017). Parental engagement and early interactions with preterm infants during the stay in the neonatal intensive care unit: Protocol of a mixed-method and longitudinal study. *BMG Open, 7*, e013824. doi:10.1136/bmjopen-2016-013824

Stevens, D. C., Helseth, C. C., & Kurtz, J. C. (2010). Achieving success in supporting parents and families in the neonatal intensive care unit. In C. Kenner & J. M. McGrath (Eds.), *Developmental care of newborns and infants: A guide for health professionals* (2nd ed., pp. 161–190). Glenview, IL: National Association of Neonatal Nurses.

Stremler, R., Haddad, S., Pullenayegum, E., & Parshuram, C. (2017). Psychological outcomes in parents of critically ill hospitalized children. *Journal of Pediatric Nursing, 34*, 36–43. doi:10.1016/j.pedn.2017.01.012

Szaniecki, E., & Barnes, J. (2016). Measurement issues: Measure of infant mental health. *Child and Adolescent Mental Health, 21*(1), 64–74. doi:10.1111/camh.12105

Tooten, A., Hoffenkamp, H. N., Hall, R. A. H., Winkel, F. W., Eliens, M., Vingerhoets, A. J. J. M., & van Bakel, H. J. A. (2012). The effectiveness of video interaction guidance in parents of premature infants: A multicenter randomized controlled trial. *BMC Pediatrics, 12*, 76–97. doi:10.1186/1471-2431-12-76

Toral-López, I., Fernández-Alcántara, M., González-Carrión, P., Cruz-Quintana, F., Rivas-Campos, A., & Pérez-Marfil, N. (2016). Needs perceived by parents of preterm infants: Integrating care into the early discharge process. *Journal of Pediatric Nursing, 31*, e99–e108. doi:10.1016/j.pedn.2015.09.007

Treyvaud, K., Doyle, L. W., Lee, K. J., Roberst, G., Cheong, J. L. Y., Inders, T., & Anderson, P. J. (2011). Family functioning, burden and parenting stress 2 years after a preterm birth. *Early Human Development, 87*, 427–431. doi:10.1016/j.earlhumdev.2011.03.008

Tryphopoulos, P. D., Letourneau, N., & Ditommaso, E. (2014). Attachment and caregiver–infant interaction: A review of observational assessments. *Infant Mental Health Journal, 35*(6), 642–656. doi:10.1002/imhj.21461

Tubbs-Cooley, H. L., Pickler, R. H., Mara, C. A., Othman, M., Kovacs, A., & Mark, B. A. (2017). e hospital magnet® designation and missed nursing care in neonatal intensive care units. *Journal of Pediatric Nursing, 34*, 5–9. doi:10.1016/j.pedn.2016.12.004

Turner, M., Winefield, H., & Chur-Hansen, A. (2013). The emotional experiences and support for parents with babies in a neonatal nursery. *Advances in Neonatal Care, 13*(6), 438–446. doi:10.1097/ANC.0000000000000030

Udry-Jørgennsen, L., Pierrehumbert, B., Borghini, A., Habersatt, S., Forcada-Guex, M., Assermet, F., & Muller-Nix, C. (2011). Quality of attachment, perinatal risk, and mother infant interaction in a high-risk premature sample. *Infant Mental Health Journal, 32*(3), 306–318. doi:10.1002/imhj.20298

United Nations Human Rights. (1989). *Convention on the rights of the child*. New York, NY: U.N. General Assembly. Retrieved from http://www.ohchr.org/en/professionalinterest/pages/crc.aspx

van Manen, M. (2012). Carrying: Parental experience of the hospital transfer of their baby. *Qualitative Health Research, 22*(2), 199–211. doi:10.1177/1049732311420447

Vance, A. J., & Brandon, D. H. (2017). Delineating among parenting confidence, parenting self-efficacy, and competence. *Advances in Nursing Science, 40*(4), e18–e37. doi:10.1097/ANS.0000000000000179

Venkataraman, R., Kamaluddeen, M., Amin, H., & Lodha, A. (2018). Is less noise, light and parental/caregiver stress in the neonatal intensive care unit better for neonates? *Indian Pediatrics, 55*, 17–21. doi:10.1007/s13312-018-1220-9

Vittner, D., Butler, S., Smith, K., Makris, N., Brownell, E., Samra, H. A., & McGrath, J. M. (2019). Parent engagement correlates with parent and preterm infant oxytocin release during skin-to-skin contact. *Advances in Neonatal Care, 19*, 73–79. doi:10.1097/ANC.0000000000000558

Vittner, D., McGrath, J. M., Robinson, J., Lawhon, G., Cusson, R., Eisenfeld, L., . . . Cong, X. (2018). Increase in oxytocin from skin-to-skin contact enhances development of parent–infant relationships. *Biological Research for Nursing*, *20*(1), 54–62. doi:10.1177/1099800417735633

Wang, L., He, J. L., & Fei, S. L. (2016). Perceived needs of parents of premature infants in the NICU. *Western Journal of Nursing Research, 40*(5), 688–700. doi:10.1177/0193945916683679

Watson, G. (2010). Parental liminality: A way of understanding the early experiences of parents who have a very preterm infant. *Journal of Clinical Nursing, 20*, 1462–1471. doi:10.1111/j.1365-2702.2010.03311.x

Westrup, B. (2015). Family-centered developmentally supportive care: The Swedish example. *Archives de Pédiatrie, 22*(10), 1086–1091. doi:10.1016/j.arcped.2015.07.005

White, R. D., Smith, J. A., & Sheply, M. M. (2013). Recommended standards for newborn ICU design, 8th edition: Practice guidelines. *Journal of Perinatology, 33*(Suppl.), S2–S16. doi:10.1038/jp.2013.10

Wittkowski, A., Garrett, C., Calam, R., & Weisberg, D. (2017). Self-report measures of parental self-efficacy: A systematic review of the current literature. *Journal of Child and Families Studies, 26*, 2960–2978. doi:10.1007/s10826-017-0830-5

Zelkowitz, P., Feeley, N., Shrier, I., Stremler, R., Westreich, R., Dunkley, D., . . . Papageogiou, A. (2011). The cues and care randomized controlled trial of a neonatal intensive care intervention: Effects on maternal psychological distress and mother-infant interaction. *Journal of Developmental and Behavioral Pediatrics, 32*(8), 591–599. doi:10.1097/DBP.0b013e318227b3dc

Zhang, X., Kurtz, M., Lee, S.-Y., & Lui, H. (2014). Early intervention for preterm infants and their mothers: A systematic review. *Journal of Perinatal and Neonatal Nursing*. Advance online publication. doi:10.1097/JPN.0000000000000065

CHAPTER 36

Palliative and End-of-Life Care

Carole Kenner and Donna J. Ryan

INTRODUCTION

In the neonatal intensive care unit (NICU), the assurance that "everything possible is being done" often is interpreted as meaning that the patient is receiving state-of-the-art technologic care. Yet the healthcare system fails both infants and their families when death occurs. The failure lies not in the infant's death itself, but rather in the neglect to emphasize state-of-the-art palliative care. Until it is evident that all dying infants receive highly skilled palliative care, as well as advanced technologic care, modern medicine cannot say that the best possible care has been provided to these infants and their families. This chapter focuses on the care of infants and their families who are facing life-threatening illnesses or are dying and the urgent need for exemplary neonatal and pediatric hospice and palliative care programs.

ETHICAL OBLIGATION TO PROVIDE OPTIMUM END-OF-LIFE CARE

It can be argued that all members of the healthcare team have an ethical obligation to plan and implement end-of-life (EOL) care; to provide highly skilled care at all times except at the EOL is to ignore the essence of comprehensive healthcare. The ethical dimensions of neonatal EOL care include an obligation to provide compassionate care; autonomy; beneficent and nonmaleficent care, especially in regard to infant pain; respecting family values, and in the provision of treatment options; justice in ensuring equitable access to care and resources; dignity in being treated with respect and honor; and truthfulness and honesty in providing information in a gentle, sensitive, and compassionate manner (Thaxton, Carter, & Dang Hornic, 2016).

Compassionate Care at the EOL

More than two decades ago, Pellegrino and Thomasma (1993) argued that healthcare professionals have a special responsibility to provide compassionate care at the EOL. They identified compassion and temperance as among the essential virtues of medical practice and cautioned against overuse of high-technology equipment in place of human engagement with patients. They noted that particularly at the EOL, healthcare professionals can become so focused on technologic processes that they use them as "substitutes for human and compassionate care."

Palliative Care Globally and Nationally

Palliative care is a global issue especially in the pediatric population. The World Health Organization (WHO) estimates that there are 1.2 million children in the world who are in need of palliative care (WHO, 2014). Variations in how children with life-threatening illnesses are treated are sometimes linked to cultural values and beliefs around the concept of death. Other barriers to access to such care are related to health policies (Fowler-Kerry, 2012). Fowler-Kerry outlines a paradigm for pediatric palliative care emerging on a global stage. A study of childhood deaths in Canadian hospitals found that the acuity of care was high before death and that most of the decisions about EOL issues were made very close to the actual time of death (McCallum, Byrne, & Bruera, 2000). In that study, most of the children were intubated at death (73%), and most died in the intensive care unit (ICU; 83%). Even today, infants in the NICU frequently die while still intubated and connected to various pieces of equipment.

In the United States, most pediatric deaths also occur in hospital ICUs (Kerr, 2001), and there is evidence that children often suffer needlessly before death (Stephenson, 2000; Wolfe et al., 2000). Most of these deaths take place in hospitals. According to the Centers for Disease Control and Prevention (CDC), the infant mortality rate in the United States in 2015 was 5.9 deaths per 1,000 births (CDC, 2018). These figures have implications for neonatal care.

Since the late 1990s when this study was done, some progress has been made in the creation of policies and procedures (Carter et al., 2004). Books are available on the subject to guide the practitioner in working with children and their families during this very difficult period of their life (Carter, Levetown, & Friebert, 2011). Catlin and Carter (2002) developed a palliative care protocol that has assisted many perinatal and neonatal centers in the development of policies to assist with EOL and palliative care issues. Rogers, Babgi, and Gomez (2008) developed an education program to address issues of moral distress in NICU nurses and in 2010, the National Association of Neonatal Nurses (NANN, 2010) published a position statement "NICU Nurse Involvement in Ethical Decisions (Treatment of Critically Ill Newborns)." Additionally, NANN (2015) in their 2015 position statement "Palliative and End-of-Life Care for Newborns and Infants," Kenner, Press, and Ryan (2015), and the American Academy of Pediatrics (AAP, 2013) have recommended practices for neonatal palliative care. Despite all of these resources to health professionals, many

providers remain uncomfortable discussing palliative care with families because their focus has always been on saving lives (Kenner et al., 2015).

New approaches must be taken to establish compassionate EOL care for all infants in the NICU. This challenge is intensified in a system in which healthcare professionals are oriented toward active intervention with technologic devices rather than toward an acceptance of death (Jecker & Pagon, 1995; Kenner & Boykova, 2010). "Palliative care is still an option often offered too late and rarely delivered in an integrated approach" (Kenner et al., 2015, p. S10). Often, many disciplines offer advice, unaware of what has already been conveyed to parents (Kenner et al., 2015). Cortezzo, Saunders, Brownell, and Moss (2013) found that palliative care education was deemed important and needed among healthcare providers and discovered that barriers included emotional difficulties, staff disagreements, and difficulty forming palliative care teams. Cortezzo et al. (2013) further reported that palliative care teams or staff bereavement groups were willing to initiate palliative care and had more positive views or experiences. However, they recommended that further exploration of differing views of palliative care among interdisciplinary team members is needed. Tan, Docherty, Barfield, and Brandon (2012) found that "anticipatory support initiated prior to the death of an infant can help parents experience a smoother transition from caring for their ill baby to coping with the actual death and aftermath" (p. 579). A study that implemented a quality of life program to evaluate moral distress in healthcare providers found that after implementation of the Pediatric Quality of Life Program, nurses and other providers encountered morally distressing situations less often (Brandon, Ryan, Sloan, & Docherty, 2014). The researchers further discovered that providers felt they had greater comfort with, and competence in, providing care focused on patients' quality of life after completing the program. Brandon et al. (2014) recommended that as "palliative care programs include many activities that reduce moral distress, nurses should actively participate in debriefing sessions and staff education to maximize their work quality of life" (p. 189). Healthcare providers should also take into consideration the bereaved families that may lack support during a sudden and unexpected perinatal loss (Gold, Tredwell, Mieras, & Laventhal, 2017), and any lack of agreement that might exist among health professionals and parents regarding palliative care.

Regardless of the setting, the goal should be to provide family-centered perinatal and neonatal palliative care and support to bereaved families experiencing anticipated or unanticipated life-limiting conditions or death of their infant (Kenner et al., 2015). Wolfe (2000) identified the "principle of family" in pediatric EOL care: that is, an obligation to treat the whole family. Wolfe (2000) saw the healthcare staff as having an ethical obligation to "pursue comfort aggressively" and to fully engage the parents in the decision-making process for their child.

The interprofessional team needs to be informed of the parents' choices, so care can be coordinated and the family's wishes are carried out (Kenner et al., 2015). Perinatal loss needs to be acknowledged as a unique type of bereavement that will require bereavement care. "Advances in genetics and technology enable many families to know well in advance that their fetus has a potentially life-limiting condition" (Kenner et al., 2015, p. S20). In either anticipated or unanticipated losses, efforts should be made to include families as part of the decision-making process.

Cultural Influences

For culturally competent care to reflect the complexity of care to support the infant and family, the nurse must be sensitive to cultural, ethnic, and religious values and must adapt and individualize care (Thaxton et al., 2016). Families need to be provided options of memory making, and asked if there is a ritual that is important to their cultural or belief system (Kenner et al., 2015). Footprints, handprints, a lock of hair, a receiving blanket, photos, and special keepsake boxes are examples of mementos related to the baby's hospital stay and provide parents with options for remembering their baby, although these may not be acceptable in some cultures (Kenner et al., 2015). Photographs provide visual proof of the reality of their baby's life and can be valuable in the mourning process (Kenner et al., 2015). "Dressing the baby is important, so the family has a photo or mental picture of their baby and not one that is naked connected to tubes and wires" (Kenner et al., 2015, p. S21). Parents should also be offered peer-to-peer support or referred to a regional or national parent support organization if there are no functioning peer support programs (Kenner et al., 2015).

Palliative care can be delivered within the NICU or special care unit, an ambulatory care center in the community or the home. Despite the reality that very few pediatric hospice groups exist and fewer for the neonate and family, Catlin found that many infants stay 6 months or longer in the hospital with 20% of the NICU infants transferred to the pediatric intensive care unit (PICU) to die even when care is futile (as cited in Thaxton et al., 2016).

Some settings are developing a connection with perinatal hospices when a problem is detected prior to delivery that may result in a stillborn or "born dying" infant. One example of this is "Alexander's House" in Kansas City, Missouri (Pearce, 2006). Children's Hospital Medical Center, Cincinnati, Ohio, developed a perinatal hospice program called "Star Shine Hospice," another example of a hospice specifically focused on children (for more information, see www.cincinnatichildrens.org/service/s/starshine/default). Many families decide to take their baby home to die. Assessment of the family's ability to cope, what support systems will be in place, and whether palliative care or hospice care for families and neonates is available in their community is recommended before being discharged from the hospital (Kenner et al., 2015). Additional stress will occur if technology is used at home to care for a medically fragile and technology-dependent infant (Carnevale, Alexander, Davis, Rennick, & Troini, 2006).

Obligation to Provide Beneficent Care

The widely accepted ethical principle of beneficence requires that healthcare professionals actively provide care that directly benefits their patients. As defined by Beauchamp and Childress (2001), the principle of beneficence encompasses both positive beneficence and actively providing benefit and utility, which requires a balancing of benefits and adverse effects. Professional codes of ethics require that nurses and physicians act in a manner that benefits those entrusted to their care. Healthcare professionals therefore are obligated to examine their actions with regard to intended beneficial outcomes while simultaneously considering the drawbacks or adverse consequences of their actions.

Obligation of Nonmaleficence

Healthcare professionals also have a legal and moral obligation to avoid inflicting harm on their patients (Beauchamp & Childress, 2001). Adherence to this ethical principle, known as nonmaleficence, may encompass the provision of life-sustaining treatment, as well as the cessation of such treatment. For example, when a treatment ceases to provide the intended benefit for a patient, it may be considered futile, and the healthcare professional therefore

is no longer obligated to continue that treatment (Beauchamp & Childress, 2001). It also refers to the adequate management of pain and not inflicting undue harm from inadequate management.

Healthcare professionals who continue to provide futile and burdensome treatments may be viewed as doing more harm than good. The distinction is made by meticulously balancing the benefits and burdens to the patient. For critically ill infants in the NICU, procedures or treatments can be considered inhumane if they inflict pain or discomfort on the infant without actual benefit (Jecker & Pagon, 1995).

Despite these arguments for humane care, burdensome, futile treatments sometimes still are given in the NICU. Weir (1984, 1995) has argued that death should not be considered the worst outcome for some infants, particularly when the chances for survival are remote or when physiologic survival is accompanied by unrelieved pain and suffering. In such cases, healthcare providers may be merely prolonging dying.

Recognition of Parents' Moral Authority

Parents have both the legal and moral authority to serve as surrogate decision makers for their infants. A growing body of literature supports parental decision-making authority, particularly for extremely premature or near-viable infants (Ho, 2003; Jecker & Pagon, 1995; Manning, 2005; Pinkerton et al., 1997; Raines, 1996); however, few studies have examined ways to empower parents to exercise this authority fully. Furthermore, a body of literature written by both parents and healthcare professionals suggests that parents may not be involved adequately in decisions about prolonged, aggressive treatments for their infants (Harrison, 1993; Pinch & Spielman, 1993, 1996; Raines, 1996; Stinson & Stinson, 1979). It can be argued that parents may not be as fully involved in decisions about their infant's care as they would like and have the authority to be, especially in cases in which aggressive therapies are of uncertain benefit to the infant. As Catlin and Carter (2002) point out, the real need in these instances is clear communication with parents and an understanding of how they wish to be involved in these decisions.

A consensus is growing among ethicists, clinicians, and families that when the benefits of life-sustaining therapies are questionable, parental involvement in treatment decision making is an ethical imperative (Harrison, 1993; Jakobi, Weissman, & Paldi 1993; Penticuff, 1987, 1988, 1995, 1998; President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, 1983). When life-sustaining therapies have proved futile, parents and professionals often are uncertain as to how to provide EOL care. The following quote is from Robert Stinson, father of Andrew, who was born in 1976 at 24 weeks' gestation. At that time, Andrew's survival was unprecedented. He underwent intensive care for 6 months, was critically ill throughout this time, and was resuscitated numerous times before his death.

> What they never understood was that one can care deeply enough about a child like Andrew to want his misery ended. Allowing Andrew to die naturally was what we wanted for him, not just to him. I thought often, when I did go in to see him, about his massive pain. He was sometimes crying then; a nearly soundless, aimless cry of pain, undirected and unlistened to except, I sometimes thought, by me. As often as I wanted to gather him into my arms, I wanted him to be allowed to die. What is the name for that? (Stinson & Stinson, 1979)

Although the Stinsons' experience occurred many years ago, evidence suggests professionals do not always incorporate the parental perspective into care decisions (Harrison, 1993; King, 1992; Mehren, 1991; Pinch & Spielman, 1996; Raines, 1996), particularly with regard to burdensome, futile treatments (Yellin et al., 1998).

There can also be differences between mothers and fathers in their reaction to the loss of their infant. Mothers often feel like they failed as a woman to produce a healthy child or they feel guilty because they blame themselves even if they did not do anything to cause the premature delivery or congenital anomaly. Fathers often feel like they failed to protect their family (Kenner et al., 2015). Either mother or father may be reluctant to share their feelings with each other and mothers may be more accepting of support groups and counseling than fathers (Kenner et al., 2015).

Burden of Treatment

The burden of treatment experienced by extremely premature infants in the NICU, especially those with minimal chance for survival, requires further ethical examination. In a national survey of physicians certified in neonatal-perinatal medicine, Yellin et al. (1998) found that many neonatologists believe that "there is an ethical or legal obligation to perform treatments that are not in the infant's best interests, regardless of parental preference." Yellin and coworkers concluded that because some neonatologists are unwilling to withdraw treatments, they may be overtreating some infants in the NICU. Unfortunately, this situation has not changed that much today (Kenner & Boykova, 2010).

Penticuff (1998) identified harm that ensues for infants, families, the healthcare team, and society when there is no accepted definition of futility. Such harm includes "needless infant suffering through prolongation of the process of dying" and "psychologic entrapment of the medical team and the family," in which initial aggressive therapies lead inexorably to more aggressive therapies, with death as the only stopping point. An example is the controversy around treatment options for children with trisomy 13 and 18 where mixed opinions exist about how far treatment should go and how parents must be included in the decision making including decisions about palliative care (Carey, 2012).

Brody, Campbell, Faber-Langendoen, and Ogle (1997) call for compassionate clinical management during the withdrawal of intensive life-sustaining treatment for adult patients using a strategic approach with well-defined goals that dictate the plan of care. Once the goals have been identified, the team examines both the benefits and the burdens of the proposed treatment plan with the family. With this approach, any treatment that is more burdensome than beneficial is limited or eliminated. Brody and coworkers identified pain and discomfort as components of treatment burden and said that there is "no sound rationale for withholding adequate analgesia or sedation" during EOL care. This is an area that requires further examination as it relates to critically ill neonates at the EOL.

The Institute of Medicine identified five core competencies that guide patient care. These are patient-centered care, interdisciplinary teams, evidence-based medicine, quality improvement, and information technology (Greiner & Knebel, 2003). All these competencies have relevance to palliative care, as it is patient and family focused and requires an integrated interprofessional team approach to provide quality care. Mullins et al. (2012) conducted a study funded by the National Institute for Nursing Research (NINR; 1 R21 NR010103-01A1) that examined the needs of parents of children newly diagnosed with cancer. Findings supported the needs parents had for clear messages from the healthcare team, and for information to support positive coping and decrease stress (Mullins et al., 2012).

COMFORT CARE AT THE EOL

Palliative care includes optimum symptom relief for the neonate, regardless of the length of life or the place the life is lived (Thaxton et al., 2016). There are always interventions that can be used to promote comfort during EOL care for infants with complex chronic conditions (Thaxton et al., 2016).

Only limited research is available on the provision of analgesia and sedation for infants at the EOL. One study focused on medications administered during life-support (e.g., ventilator) withdrawal. Partridge and Wall (1997) conducted a retrospective chart review to examine the practice of opioid analgesia administration in one NICU at the time of life-support withdrawal. **Emergency Alert: Despite growing concern over opioid use, pain management including opioids is essential for babies who are potentially dying**. They found that of infants who had a known painful condition (e.g., acute abdominal or surgical pain) and were receiving analgesia before the decision was made to withhold further life-sustaining treatment, 84% received opioid analgesia during life-support withdrawal. An interesting finding of this study was that the infants who did not receive any analgesia at the time of life-support withdrawal had also not received any pain medication before the decision was made to discontinue life support. These findings suggest that analgesia is not being given to ease the possible suffering associated with withdrawal of life support, but rather to manage specific disease processes. (Additional aspects of neonatal pain management are discussed in Chapter 23.) It is recognized that even the smallest of patients have rights, and these include palliative care.

PEDIATRIC HOSPICE CARE

The use of hospice and palliative care has made a significant difference in EOL care for adults. Its primary focus while still supporting life is care, not cure (Friebert & Williams, 2015). According to the National Hospice and Palliative Care Organization (NHPCO; 2001, 2018a), hospice care can be provided in select hospitals, in individual hospice facilities, or in a person's home. In 2013, the AAP Section on Hospice and Palliative Medicine and Committee on Hospital Care published a paper outlining the care commitments and recommendations for pediatric palliative and hospice care programs. These recommendations included that interdisciplinary trained teams are available to provide this care, if the child is in a large institution (AAP, 2013). This type of care is considered a critical component of quality care and facilitates safe care. **Quality and Safety Issue: Family support, as well as compassionate care with consideration of family wishes and cultural values, is important.**

> Reliable statistics for children who receive PP/HC services remain difficult to parse from existing sources. It is also difficult to characterize children who might be appropriate or eligible for services because this characterization is a moving target. Variations in chronological, definitional, and prognostic criteria, as well as accessibility to establish programs, hinder accurate descriptions of this population. (Friebert & Williams, 2015, p. 4)

"As with adults, most children are still dying in the hospital, and most in an intensive care unit (ICU) setting. In a prospective, observational cohort study of all patients served by six hospital-based pediatric palliative care programs, 44.6% of patients were cared for in a home or hospice facility. Most patients (62%) who died did so in a hospital setting while 36.6% died at home or in a hospice facility" (Feudtner et al., 2011, as cited by Friebert & Williams, 2015, p. 6). A study conducted by Children's International Project on Palliative/Hospice Service (ChiPPS, now referred to as Children's Project on Palliative/Hospice Services) found that only a small percentage of children who could have benefited from palliative or hospice care were actually provided this care (5,000 out of 53,000) and most very late in their disease (NHCPO, 2001). Awareness of the need for hospice and palliative care in the neonatal/pediatric population is growing. About 69% of the U.S.-based children's hospitals have palliative care teams and 30% offer home visits (Freudtner et al., 2013).

Barriers to Pediatric Hospice Service

Unfortunately, there are many barriers to the availability and provision of hospice care to ill children and families who could benefit from it. The NHPCO (2000) described psychologic, financial, educational, and regulatory barriers to pediatric palliative care. One of the psychologic barriers is the association of palliative care with the concept of giving up or going against hope (Kenner & Boykova, 2010). Families often avoid palliative care, rather than identifying with the life-enhancing benefits it offers. Financial barriers arise because the home-based, multidisciplinary care is often not reimbursed. The educational barriers for care providers are evident in the lack of palliative care training for most physicians and the avoidance of discussing hospice care with parents (Moody, Siegel, Scharbach, Cunningham, & Cantor, 2011). Some of these training issues can be addressed through simulated difficult conversations (Brown, Lloyd, Swearingen, & Boateng, 2012). Regulatory barriers also exist because the reimbursement system is based on the needs of adults. Ignoring the differences in care needs between children and adults creates barriers to hospice as an option for many families.

PEDIATRIC PALLIATIVE CARE

The AAP issued guidelines in 2000 for the care of children with life-threatening and terminal conditions. The AAP recommended palliative care for infants when "no treatment has been shown to alter substantially the expected progression toward death." According to the AAP guidelines, palliative care incorporates control of pain, symptom management, and care of the psychologic, social, and spiritual needs of children and their families. The AAP also has established five principles of palliative care: (a) respect for the dignity of patients and families, (b) access to competent and compassionate palliative care, (c) support for the caregivers, (d) improved professional and social support for pediatric palliative care, and (e) continued improvement of pediatric palliative care through research and education. There is a section on Hospice and Palliative Medicine within the AAP that is updated on a regular basis. This section upholds the AAP (2000) guidelines and reinforces the need to enhance the quality of life for the child and family. It also stresses care coordination and a team approach while carrying out the five previously listed principles of care (AAP, 2013).

Respect for the Dignity of Patients and Families

Respect for patients' and families' dignity means that information about palliative care should be provided, and the parents' ability to make their own choice of a program should be respected. Also, the plan of care must incorporate and respect the parents' expressed wishes for their child's care, specifically with regard to testing, monitoring, and treatment (AAP, 2000). This respect should consider religious beliefs and cultural values.

Access to Competent and Compassionate Palliative Care

Compassionate palliative care includes alleviation of pain and other symptoms and access to supportive therapies, such as grief counseling and spiritual support. This principle includes provision of adequate respite care for parents (AAP, 2000; Goldman, Hain, & Liben, 2012).

Support for the Caregivers

The AAP recognizes the importance of support for healthcare professionals involved in the child's care. This support may include paid funeral leave, peer counseling, or remembrance ceremonies (AAP, 2000).

Improved Professional and Social Support for Pediatric Palliative Care

The barriers discussed in this chapter can prevent families from obtaining pediatric palliative care. Healthcare professionals must help families overcome these obstacles (AAP, 2000).

Continued Improvement of Pediatric Palliative Care Through Research and Education

Healthcare professionals need continuing education on ways to provide comprehensive palliative care. Also, research that focuses on the effectiveness of palliative care interventions and on models of pediatric palliative care delivery is needed (AAP, 2000). The creation of End-of-Life Nursing Education Consortium (ELNEC) training through the City of Hope and the American Association of Colleges of Nursing (AACN, 2018) has helped facilitate hospital-based nurses, nurse faculty, and, in turn, students to learn palliative care principles. The ELNEC modules can be used in undergraduate and graduate curricula as a part of any clinically based management course or in a standalone elective. The NHPCO (2018b) has a similar program called EPEC-end-of-life care that focuses on interdisciplinary palliative care training. Both of these programs are train-the-trainer models.

Incorporating Pediatric Palliative Care Into the NICU

The AAP recommends that palliative care begin at the time of diagnosis of a life-threatening or terminal condition (AAP, 2000). In the NICU, particularly for extremely premature neonates and for neonates with life-threatening anomalies, palliative care should begin at the time of admission. For many healthcare professionals, this requires a rather dramatic shift from providing intensive high-technology care to providing intensive palliative care. This is in direct contrast to another common tenet of neonatal care: that is, that discharge planning should begin upon admission. At times, particularly during the early diagnostic phase, palliative care can be provided along with technologic care; this arrangement allows the staff to focus on symptom management and pain control while weighing the benefits and harm of treatment. It also provides for interdisciplinary team members who can provide the support the family needs.

Often, when a neonate is born at the edge of viability, the clinical course shows a downward trend. The neonate's physiologic parameters cause concern as evidence mounts that the organ systems are failing. This scenario represents the inevitable point at which intensive efforts to prolong life merely serve to prolong the infant's dying. In such cases, both infants and their families would benefit from a smooth transition to intensive palliative care. This requires a level of skilled care that is not always present in the NICU. The care providers must quickly recognize the futility of sustained therapies and must be expert at providing palliative care to both infant and family. Unfortunately, as research has indicated, all too often infants and children die while still intubated (McCallum et al., 2000); suffer from pain that is inadequately controlled or untreated (Kenner & Boykova, 2010; Partridge & Wall, 1997); and have not received the benefits of palliative care measures (Byock, 1997; Goldman, 1998; Rushton, 2000; Stephenson, 2000). The NANN, the Association of Pediatric Oncology Nurses (APON), and the Society of Pediatric Nurses (SPN) have stated that this area of neonatal care is very important. Under the auspices of the National Leadership Academy on EOL Issues, which is sponsored by Johns Hopkins University, these three organizations are adapting the Last Acts Precepts (https://www.caringcommunity.org/helpful-resources/models-research/last-acts/) for neonatal and pediatric patients. The Last Acts organization provides support for healthcare professionals and families through publications and taking action on EOL issues. It believes that appropriate language must be included to reflect cases such as an infant who is literally born dying, as well as the family's unique needs in such cases. This collaboration is a milestone in efforts to recognize that neonatal and pediatric patients and their families deserve the same level of care that adults have received.

Worldwide recognition of the need for neonatal and pediatric palliative care is growing, thanks to funding from the Soros Foundation, the Robert Wood Johnson Foundation, City of Hope, Johns Hopkins University, the Association of American Colleges of Nursing, and other organizations that support educational efforts about EOL and palliative care. Nursing curricula are being revised to include content and competencies on EOL care. Training programs such as the ELNEC (www.aacn.nche.edu/elnec) are broadening nurses' knowledge in this specialty. One ELNEC training focuses specifically on the neonatal/pediatric population (AACN, 2018). Modules that focus specifically on developmental issues regarding the concept of death and dying as well as how to assess for pain in the nonverbal child help health professionals to adapt materials to their settings. Organizations such as the International Association of Hospice and Palliative Care, the NHPCO, and the Hospice and Palliative Care Nurses Association, which traditionally have focused primarily on adult issues, have begun incorporating pediatric palliative care concerns into their initiatives. The inclusion of a chapter (Kenner & Boykova, 2010) on palliative care in the NICU in Dr. Betty Ferrell's palliative care textbook—the gold standard in palliative care—will increase the awareness of the need for EOL care in this population. All these actions bode well for the integration of EOL care into customary pediatric and neonatal care as a standard that is expected and demanded.

In 2015, the National Perinatal Association under the leadership of Drs. Sue Hall and Michael Hynan invited neonatal/perinatal specialists and parents to develop program standards for psychosocial support of parents and infants admitted to an NICU (Hall et al., 2015). Part of these recommendations focused on palliative and bereavement care (Hall et al., 2015; Hynan & Hall, 2015; Kenner et al., 2015). Recommendations for NICU bereavement and palliative care (Kenner et al., 2015) can be found in Boxes 36.1 to 36.3.

Box 36.1

NICU RECOMMENDATIONS FOR PALLIATIVE AND BEREAVEMENT CARE

1. Parents who lose a baby before, during, or shortly after birth, or later in the NICU, should be offered:
   a. Anticipatory guidance regarding the grieving process, including how mothers and fathers, and other family members, may grieve differently (Wallerstedt & Higgins, 1996). This anticipatory guidance should begin antenatally if a life-limiting diagnosis has been determined (Bennett, Dutcher, & Snyders, 2011; Calhoun, Napolitanto, & Terry, 2003).
   b. Participation in bereavement rituals, including those that meet their spiritual, religious, and cultural preferences. These rituals may include a variety of practices and items that will help them remember their baby, such as provision of hand prints, foot prints, and photographs (Carter, 2004; De Lisle-Porter & Podruchny, 2009). Smooth communication should be facilitated between parents and the staff of the NICU and obstetric units throughout the dying process; a perinatal social worker or other designated person can assist with this (National Association of Perinatal Social Workers, 2007).
   c. Psychosocial support for all members of the family, including but not limited to grandparents and the baby's siblings (American Academy of Pediatrics Section on Hospice and Palliative Medicine and Committee on Hospital Care, 2013; Pearson, 1997).
   d. Peer-to-peer support and/or referral to community or Internet support organizations.
   e. Counseling regarding both the physical and psychological considerations of attempting another pregnancy (American Academy of Pediatrics Section on Hospice and Palliative Medicine and Committee on Hospital Care, 2013).
   f. Post-hospital follow-up in a variety of forms, including individual contact by a staff member at various time periods as well as a conference 4–6 weeks after the baby's death to review autopsy and other results that will help parents understand what happened to their baby (Levetown, 2008).
2. When intensive care will not be provided, a collaborative, interdisciplinary approach should be used to provide palliative care including bereavement care to any family whose fetus or neonate is facing a life-limiting condition or imminent death (Aladangady, & de Rooy, 2012).
3. Physicians and nurse practitioners should follow the guidelines outlined by the American Academy of Pediatrics when engaging in discussions with parents about whether to initiate or continue intensive care for a baby who may not survive (American Academy of Pediatrics Committee on Fetus and Newborn, 2007; Cummings, & American Academy of Pediatrics, Committee on Fetus and Newborn, 2015); neonatal nurses and perinatal social workers should be included in the decision-making process as well (National Association of Neonatal Nurses, 2010; National Association of Perinatal Social Workers, 2007). Intensive care should be provided only if it is believed that the baby will benefit from it. The best interests of the baby should be the guiding standard (American Academy of Pediatrics Committee on Fetus and Newborn, 2007; Cummings, & American Academy of Pediatrics, Committee on Fetus and Newborn, 2015).
4. In cases where there are disagreements between parents and the healthcare team when making end-of-life decisions, particularly around the futility of further care for a baby, a bioethics consult should be obtained and/or the case presented to the hospital Bioethics Committee (American Academy of Pediatrics Committee on Fetus and Newborn, 2007).
5. Parents whose babies with life-limiting conditions survive to hospital discharge should be offered both practical and psychosocial support to help them prepare for discharge, learn how to both care for and cope with their baby at home, (Craig & Goldman, 2003; Criag & Mancini, 2013) and/or they should be referred to a hospice with experience caring for infants. Their baby's primary care provider, neonatal specialist, medical home, or any subspecialists should be fully involved in making and carrying out home care plans and providing follow-up support.

Box 36.2

ANTENATAL RECOMMENDATIONS

Parents anticipating a perinatal loss should be offered:

1. An antenatal interdisciplinary conference to develop the following plans, which should be individualized according to parents' desires and cultural, spiritual, and religious beliefs:
   a. A birth plan, which should include parents' preferences regarding the conduct of labor, the circumstances surrounding delivery, and the care for baby and parents after the baby's birth;
   b. A plan for the extent of resuscitation to be performed and whether to allow a natural death; and
   c. A palliative care plan as indicated and desired when babies are not expected to survive. This plan should include parents' preferences on where the baby's care will be delivered, how nutrition will be provided, and how baby's pain and discomfort will be managed (Craig & Goldman, 2003; Criag & Mancini, 2013).
2. Encouragement to bond with their baby and to create memories throughout the pregnancy whenever feasible, recognizing the barriers parents may face in bonding.
3. Psychosocial support for all members of a family, including grandparents and the infant's siblings.
4. Both practical and psychosocial support to help parents cope with their baby at home when infants with life-limiting conditions survive to hospital discharge (American Academy of Pediatrics Section on Hospice and Palliative Medicine and Committee on Hospital Care, 2013).

Box 36.3

HEALTH SYSTEM RECOMMENDATIONS

1. All health professionals who work with pregnant women, neonates, and their families should receive education and demonstrate competence in palliative and bereavement care that is appropriate within their scope of practice. This education should include training in how to communicate effectively and empathetically with families (American Academy of Pediatrics Section on Hospice and Palliative Medicine and Committee on Hospital Care, 2013; Boss, Hutton, Donohue, & Arnold, 2009; National Association of Neonatal Nurses, 2015).
2. Policies for palliative care and bereavement practices in any part of a healthcare system should be in place and easily accessible to all staff, to ensure a standard of care for all families.
3. Palliative and bereavement care resources in the community should be available to anyone who is providing care to a neonate and family facing a life-threatening condition or imminent death or has experienced a loss, whether or not there is a palliative care team or program at a specific institution.
4. Hospitals should work in partnership with their local organ donation organizations to determine whether specific babies are eligible to become organ donors and to assess, in collaboration with the family, whether organ donation is the right choice for them.
5. Healthcare staff who provide palliative and/or bereavement care should receive psychosocial support and engage in self-care (Sanchez-Reilly, Morrison, Carey, Bernacki, O'Neil, & Kapo, 2013), to enable them to provide optimal care to the families they serve, as well as to prevent burnout, compassion fatigue, or secondary traumatic stress (American Academy of Pediatris Section on Hospice and Palliative Medicine and Committee on Hospital Care, 2013). The perinatal social worker (De Lisle-Porter, & Podruchny, 2009), NICU psychologist (Gold, Dalton, & Schwent, 2007), or pastoral care staff (Sharp, 1991) can be instrumental in providing this support.

Source: Copyright permission granted by authors Kenner and Ryan; Nature Publishing. Kenner, C., Press, J., & Ryan, D. (2015). Palliative and bereavement care: A family centered integrated approach. *Journal of Perinatology, 35*, S19–S23. doi:10.1038/jp.2015.145

BEREAVEMENT

Grief is unique to each individual and varies in expression, duration, and meaning. Parents often move through the grief process differently. The infant's mother may express her grief by crying, whereas the father may express his grief by isolating himself.

For many parents, grief is a lifelong process. Significant life events can trigger grieving, as can such routine childhood milestones as seeing a neighbor's child get on the school bus for her first day of kindergarten or, many years later, receiving a high school graduation announcement for what would have been their child's class.

As parents progress through the first year after their loss, it is important to prepare them for the grief they are likely to experience in the future and to help them develop a plan for themselves. Every family is unique and determines their own milestone days, those days that bring special remembrance of their child. Milestone days may include the child's birthday, the anniversary of the child's death, or holidays. It sometimes is helpful for parents to schedule time off on these milestone days so that they can plan a special activity. Some parents may want to be alone and take a quiet walk together. Others may prefer to be surrounded by relatives or a few close friends. Still others may want to spend the day with another parent who has experienced similar grief.

The nurse should stress three important points to bereaved families: (a) grief is individualized; (b) grief is a process; and (c) family members should not hesitate to seek assistance with their grief, even years after the child's death.

SUMMARY

Even when death approaches quickly in the NICU, measures can be taken to ease the infant's transition and adequately assist the family. It is no longer enough to provide quality bereavement and postmortem care to infants and their families. Research into and evaluation of care guidelines are needed so that infants can receive the same quality of EOL care afforded to other members of society. Neonatal nurses have been at the forefront of this movement and now have the opportunity to serve as leaders in the design and implementation of exemplary neonatal palliative care programs.

CASE STUDY

An infant was born at 24 weeks' gestation to a family that had just moved to a new city and had no relatives in the area. This was a first baby for the family. Shortly after birth, it was recognized that the infant would probably not survive because, in addition to being premature, overwhelming sepsis was present. The care team (without the family) met. Some felt that the family needed to be given options immediately to call the palliative care team in for a discussion of treatment options, while other team members believed that a few more days should be given to the baby to see how the infant would respond to ventilation and antibiotic therapy. A consultation was done with the palliative care team that convinced the neonatal team to talk with the family, describe the infant's status, discuss the possible course, and ask them to be part of the team to make decisions about palliative care and in what form—in other words, how aggressive they wanted the treatment to be, how in either case palliative care would be provided, how care would be coordinated, and how they as a family would be supported irrespective of the outcome. Over the course of the next week, the infant continued to get progressively sicker, the family was supported by the palliative care team, and relatives were contacted via Internet to ensure they could support the family and see the baby. The family planned the care and eventually made the decision to take the infant, whom they named Sarah Elizabeth, off the ventilator. They held and rocked the baby surrounded by staff they selected until the moment of death. The death was peaceful, and the palliative care team continued to follow up with the family for the next month. The team also debriefed the neonatal caregivers who worked closely with the family to ensure they were supported. The principles of dignity, respect, and need for caregiver support for both the family and professional staff were upheld.

EVIDENCE-BASED PRACTICE BOX

Much progress has been made since the early 2000s when protocols for perinatal and neonatal palliative care appeared. An instrument called the Perinatal Palliative Care Perceptions and Barriers Scale Instrument was developed by Drs. Charlotte Wool and Sally Northam. This instrument was developed and validated over time for use with nurses and physicians. The focus is to determine perceptions of the health professionals in order to develop staff/faculty training programs with the ultimate goal to provide better support of patients and families. This instrument can be used in a variety of ways and needs further testing to broaden its use.

Source: From Wool, C., & Northam, S. (2011). The Perinatal Palliative Care Perceptions and Barriers Scale Instrument©: Development and validation. *Advances in Neonatal Care, 11*(6), 397–403. doi:10.1097/ANC.0b013e318233809a

PARENT VOICES

Amy Blanchard

After we realized our daughter was not going to get better, my husband and I met with the palliative care team. This team included the chaplain, pain management team, and the social worker. The most important thing for nurses to do is not to act like the baby has already passed away. Know that she is still alive and the parents are in the process of making life decisions for their child. We had some phenomenal nurses who treated our daughter like their own. That absolutely meant the world to us. We were comfortable leaving our daughter in their capable hands. Having a care team of nurses was one of the most important aspects of Molly's nursing care. These nurses not only cared for and loved our daughter, but also us (her parents) as well.

During palliative care, we would ask for the nurses' opinions. They knew our daughter almost as well as we did. They knew how certain medications affected her and if she was in pain. We valued their opinion in regard to some of the care that she received during the end. They wanted Molly to be pain free and as comfortable as we wanted her to be.

I will always remember the last day of my daughter Molly's life like it was yesterday. Discontinuing care was the hardest decision my husband and I have ever had to make. On that day, we were able to call two of our favorite nurses from Molly's care team. They were not scheduled to work but came to Molly's room to say their goodbyes. They sat with us and cried with us while we held our daughter for the last time. These two nurses gave my sweet baby girl her last bath when I was not able to. They were angels who flew in and took over when I myself was an emotional wreck. I'll be forever grateful for Molly's loving nurses.

To some families, like mine, NICU nurses should know that they are not just a nurse. They are also caretakers to the baby's parents. They will cry along with mothers and fathers and when a baby passes away, they are the first ones the parents may want to see. A strong bond forms when your baby spends 4 to 5 months with a nurse. I hope these nurses know that they will forever be a part of some family's lives, even if the baby passes away and the family no longer visits. These nurses will be remembered always.

ONLINE RESOURCES

American Association of Colleges of Nursing. (n.d.). *ELNEC-pediatric palliative care.* Retrieved from http://www.aacnnursing.org/ELNEC

Center fo Advance Palliative Care. (n.d.). *IPAL-ICU project.* Retrieved from http://www.virtualhospice.ca/en_US/Main+Site+Navigation/Home/For+Professionals/For+Professionals/Tools+for+Practice/Communication/IPAL_ICU+Project.aspx

Center to Advance Palliative Care. *IPAL improving palliative care.* Retrieved from https://www.capc.org/

The Center to Advance Palliative Care Palliative Care Tools, Training & Technical Assistance. Retrieved from http://www.capc.org/

Hospice and Palliative Care Nurses Association, Hospice and Palliative Credentialing Cenger, and Hospice and Palliative Nurses Foundation: Advancing expert care. Retrieved from https://advancingexpertcare.org

NICU Helping Hands. Retrieved from https://www.nicuhelpinghands.org

Now I Lay Me Down to Sleep. Retrieved from https://www.nowilaymedowntosleep.org

Perinatal Hospice and Palliative Care: Continuing your pregnancy when your baby's life is expected to be brief. Retrieved from https://www.perinatalhospice.org

Preemie Parent Alliance. Retrieved from https://preemieparentalliance.org

Preemie World. Retrieved from https://preemieworld.com

REFERENCES

Aladangady, N., & de Rooy, L. (2012). Withholding or withdrawal of life sustaining treatment for newborn infants. *Early Human Development, 88*(2), 65–69. doi:10.1016/j.earlhumdev.2012.01.002

American Academy of Pediatrics. (2000). Palliative care for children. *Pediatrics, 106*(2), 351–357. doi:10.1542/peds.106.2.351

American Academy of Pediatrics Committee on Fetus and Newborn. (2007). Noninitiation or withdrawal of intensive care for high-risk newborns. *Pediatrics, 119*(2), 401–403. doi:10.1542/peds.2006-3180

American Academy of Pediatrics, Section on Hospice and Palliative Medicine and Committee on Hospital Care. (2013). Pediatric palliative care and hospice care commitments, guidelines and recommendations. *Pediatrics, 132*(5), 966–972. doi:10.1542/peds.2013-2731

American Association of Colleges of Nursing. (2018). *End-of-Life Nursing Education Consortium*. Retrieved from http://www.aacnnursing.org/ELNEC

Beauchamp, T. L., & Childress, J. F. (2001). *Principles of biomedical ethics* (5th ed.). New York, NY: Oxford University Press.

Bennett, J., Dutcher, J., & Snyders, M. (2011). Embrace: addressing anticipatory grief and bereavement in the perinatal population: a palliative care case study. *Journal of Perinatal & Neonatal Nursing, 25*(1), 72–76. doi:10.1097/JPN.0b013e318208cb8e

Boss, R., Hutton, N., Donohue, P., & Arnold, R. (2009). Neonatologist training to guide family decision making for critically ill infants. *Archives of Pediatric & Adolescent Medicine, 163*(9), 738–788.

Brandon, D. H., Ryan, D., & Docherty, S. L. (2014). Impact of a pediatric quality of life program on providers' patterns of moral distress. *Maternal Child Nursing, 39*(3), 189–197. doi:10.1097/NMC.0000000000000025

Brody, H., Campbell, M. L., Faber-Langendoen, K., & Ogle, K. S. (1997). Withdrawing intensive life-sustaining treatment: Recommendations for compassionate clinical management. *New England Journal of Medicine, 336*(9), 652–657. doi:10.1056/NEJM199702273360910

Brown, C. M., Lloyd, E., Swearingen, C. J., & Boateng, B. A. (2012). Improving resident self-efficacy in pediatric palliative care through clinical simulation. *Journal of Palliative Care, 28*(3), 157. doi:10.1177/082585971202800305

Byock, I. (1997). *Dying well: Peace and possibilities at the end of life*. New York, NY: Riverhead Books.

Calhoun, B., Napolitano, P, & Terry, M. (2003). Perinatal hospice: comprehensive care for the family of the fetus with a lethal condition. *Journal of Reproductive Medicine, 48*(5), 343–348. doi:10.1097/01.OGX.0000093270.97479.A4

Carey, J. C. (2012). Perspectives on the care and management of infants with trisomy 18 and trisomy 13: Striving for balance. *Current Opinion in Pediatrics, 24*(6), 672–678. doi:10.1097/MOP.0b013e3283595031

Carter, B. (2004). Providing palliative care for newborns. *Pediatric Annuals, 33*(11), 770–777.

Carnevale, F., Alexander, E., Davis, M., Rennick, J., & Troini, R. (2006). Daily living with distress and enrichment: The moral experience of families with ventilator-assisted children living at home. *Pediatrics, 117*(1), e48–e60. doi:10.1542/peds.2005-0789

Carter, B. S., Howenstein, M., Gilmer, M. J., Throop, P., France, D., & Whitlock, J. A. (2004). Circumstances surrounding the deaths of hospitalized children: Opportunities for pediatric palliative care. *Pediatrics, 114*(3), e361–e366. doi:10.1542/peds.2003-0654-F

Carter, B. S., Levetown, M., & Friebert, S. E. (Eds.). (2011). *Palliative care for infants, children, and adolescents: A practical handbook* (2nd ed.). Baltimore, MD, Johns Hopkins University Press.

Catlin, A., & Carter, B. (2002). Creation of a neonatal end-of-life palliative care protocol. *Journal of Perinatology, 22*(3), 184–195. doi:10.1038/sj.jp.7210687

Centers for Disease Control and Prevention. (n.d.). Infant mortality. Retrieved from https://www.cdc.gov/reproductivehealth/MaternalInfantHealth/InfantMortality.htm

Cortezzo, D., Sanders, M., Brownell, E., & Moss, K. (2013). Neonatologists' perspectives of palliative and end-of-life care in neonatal intensive care units. *Journal of Perinatology, 33*(9), 731–735. doi:10.1038/jp.2013.38

Craig, F., & Goldman, A. (2003). Home management of the dying NICU patient. *Seminars in Neonatology, 8*(2), 177–183. doi:10.1016/S1084-2756(02)00223-3

Craig, F., & Mancini, A. (2013). Can we truly offer a choice of place of death in neonatal palliative care? *Seminars in Fetal & Neonatal Medicine, 18*(2): 93–98. doi:10.1016/j.siny.2012.10.008

Cummings, J., & American Academic of Pediatrics, Committee on Fetus and Newobrn. (2015). Antenatal counseling regarding resuscitation and intensive care before 25 weeks of gestation. *Pediatrics, 136*(3), 588–595. doi:10.1542/peds.2015-2336

De Lisle-Porter, M., & Podrunchny, A. (2009). The dying neonate: family-centered end-of-life care. *Neonatal Network, 28*(2), 75–83. doi:10.1891/0730-0832.28.2.75

Feudtner, C., Kang, T. I., Hexem, K. R., Friedrichsdorf, S. J., Osenga, K., Siden, H., . . . Wolfe, J. (2011). Pediatric palliative care patients: A prospective multicenter cohort study. *Pediatrics, 127*(6). 1094–1101. doi:10.1542/peds.2010-3225

Fowler-Kerry, S. (2012). Pediatric palliative care: A new and emerging paradigm. In C. Knapp, V. Madden, & S. Fowler-Kerry (Eds.), *Pediatric palliative care global perspectives* (pp. 449–451). Dordrecht, The Netherlands: Springer.

Freudtner, C., Wormer, J., Augustin, R., Remke, S., Wolfe, J., Friebert, S., & Weissman, D. (2013). Pediatric Care Programs in childrens' hospitals: A cross-sectional national survey. *Pediatrics*, 132(6), 1-8. Retrieved from https://pdfs.semanticscholar.org/924f/452da1411ed0bd487351a42ac173f868c413.pdf

Friebert, S., & Williams, C. (2015). *NHPCO's facts and figures: Pediatric palliative and hospice care in America*. Retrieved from https://www.nhpco.org/sites/default/files/public/quality/Pediatric_Facts-Figures.pdf

Gold, K., Dalton, V., & Schwent, T. (2007). Hospital care for parents after perinatal death. *Obstetrics & Gynecology, 109*(5), 1156–1166.

Gold, K., Tredwell, M., Mieras, M., & Laventhal, N. (2017). Who tells a mother her baby has died? Communication and staff presence during stillbirth delivery and early infant death. *Journal of Perinatology, 37*, 1330–1334. doi:10.1038/jp.2017.125

Goldman, A. (1998). ABC of palliative care: Special problems of children. *British Medical Journal, 316*(7124), 49–52. doi:10.1136/bmj.316.7124.49

Goldman, A., Hain, R., & Liben, S. (2012). *Oxford textbook of palliative care for children*. Oxford, UK: Oxford University Press.

Greiner, A. C., & Knebel, E. (Eds.). (2003). *Health professions education: A bridge to quality*. Washington, DC: National Academies Press.

Hall, S., Hynan, M., Phillips, R., Press, J., Kenner, C., & Ryan, D. J. (2015). Development of program standards for psychosocial support of parents of infants admitted to a neonatal intensive care unit: A national interdisciplinary consensus model. *Newborn and Infant Nursing Reviews, 15*(1), 24–27. doi:10.1053/j.nainr.2015.01.007

Harrison, H. (1993). The principles for family-centered neonatal care. *Pediatrics, 92*(5), 643–650. Retrieved from https://pediatrics.aappublications.org/content/92/5/643

Ho, L. Y. (2003). Perinatal care at the threshold of viability—from principles to practice. *Annals of the Academy of Medicine of Singapore, 32*(3), 362–375.

Hynan, M. T., & Hall, S. L. (2015). Psychosocial program standards for NICU parents. *Journal of Perinatology, 35*(Suppl. 1), S1–S4. doi:10.1038/jp.2015.141

Jakobi, P., Weissman, A., & Paldi, E. (1993). The extremely low birth weight infants: The twenty-first century dilemma. *American Journal of Perinatology, 10*(2), 155–159. doi:10.1055/s-2007-994650

Jecker, N. S., & Pagon, R. A. (1995). Medical futility: Decision making in the context of probability and uncertainty. In A. Goldworth, W. Silverman, D. K. Stevenson, E. W. D. Young, & R. Rivers (Eds.), *Ethics and perinatology*. New York, NY: Oxford University Press.

Kenner, C., & Boykova, M. (2010). Palliative care in the neonatal intensive care unit. In B. R. Ferrell & N. Coyle (Eds.), *Oxford textbook of palliative nursing* (3rd ed., pp. 1065–1097). New York, NY: Oxford Press.

Kenner, C., Press, J., & Ryan, D. (2015). Recommendations for palliative and bereavement care in the NICU: A family-centered integrative approach. *Journal of Perinatology, 35*, S19–S23. doi:10.1038/jp.2015.145

Kerr, E. (2001). Kids Path cares for children coping with illness or loss. *MD News Piedmont Triad, (5)*, 24–26. Retrieved from https://www.hospiceac.org/services/kids-path/

King, N. M. P. (1992). Transparency in neonatal intensive care. *Hastings Center Report, 22*(2), 18–25. doi:10.2307/3563293

Levetown, M. (2008). American Academy of Pediatrics Committee on Bioethics. Communicating with children and families: from everyday interactions to skill in conveying distressing information. *Pediatrics, 121*(5), e1441–e1460. doi:10.1542/peds.2008-0565

Manning, D. (2005). Proxy consent in neonatal care—goal-directed or procedure-specific? *Health Care Analysis, 13*(1), 1–9. doi:10.1007/s10728-005-2566-4

McCallum, D. E., Byrne, P., & Bruera, E. (2000). How children die in hospital. *Journal of Pain and Symptom Management, 20*(6), 417–423. doi:10.1016/S0885-3924(00)00212-8

Mehren, E. (1991). *Born too soon*. New York, NY: Doubleday.

Moody, K., Siegel, L., Scharbach, K., Cunningham, L., & Cantor, R. M. (2011). Pediatric palliative care. *Primary Care, 38*(2), 327. doi:10.1016/j.pop.2011.03.011

Mullins, L., Chaffin, M., Phipps, S., Hullmann, S., Fedele, D., & Kenner, C. (2012). A clinic-based interdisciplinary intervention for mothers of children newly diagnosed with cancer: A pilot study. *Journal of Pediatric Psychology, 37*(10), 1104–1115. doi:10.1093/jpepsy/jss093

National Association of Perinatal Social Workers. (2007). Standards for social work services in perinatal bereavement. Whittier, CA: National Association of Perinatal Social Workers. Retrieved from https://www.napsw.org/assets/docs/bereavement-standards.pdf

National Association of Neonatal Nurses. (2010). *NICU nurse involvement in ethical decisions (Treatment of critically ill newborns). Position Statement #3015*. Chicago, IL: National Association of Neonatal Nurses. Retrieved from http://www.nann.org/uploads/files/3015_reviewed_February_2010.pdf

National Association of Neonatal Nurses. (2010). *Position Statement #3015: NICU nurse involvement in ethical decisions (Treatment of critically ill newborns)*. Chicago, IL: Author. Retrieved from http://nann.org/uploads/About/PositionPDFS/1.4.12_Nurse%20Involvment%20in%20Ethical%20Decisions.pdf

National Association of Neonatal Nurses. (2015). Palliative and end-of-life care for newborns and infants: Position statement #3063. Chicago, IL: Author. Retrieved from http://nann.org/uploads/About/PositionPDFS/1.4.5_Palliative%20and%20End%20of%20Life%20Care%20for%20Newborns%20and%20Infants.pdf

National Hospice and Palliative Care Organization. (2000). *Compendium of pediatric palliative care*. New Orleans, LA: NHPCO.

National Hospice and Palliative Care Organization. (2001, October). *ChiPPS White Paper: A call for change: Recommendations to improve the care of children living with life-threatening conditions*. Alexandria, VA: Author.

National Hospice and Palliative Care Organization. (2018a). Pediatric hospice and palliative care. Retrieved from https://www.nhpco.org/pediatric

National Hospice and Palliative Care Organization. (2018b). The education on palliative and end-of-life care (EPEC) project. Retrieved from http://www.aacnnursing.org/ELNEC

Partridge, J. C., & Wall, S. N. (1997). Analgesia for dying infants whose life support is withdrawn or withheld. *Pediatrics, 99*(1), 76–79. doi:10.1542/peds.99.1.76

Pearce, E. W. J. (2006). *Perinatal hospice/supportive care for the dying unborn infant. Supportive voice*. Retrieved from http://www.careofdying.org/SV/PUBSART.ASP?ISSUE=SV99SU&ARTICLE=N

Pearson, L. (1997). Family-centered care and the anticipated death of a newborn. *Pediatric Nursing, 23*(2), 178–182.

Pellegrino, E. D., & Thomasma, D. C. (1993). *The virtues in medical practice*. New York, NY: Oxford University Press.

Penticuff, J. H. (1987). Neonatal nursing ethics: Toward a consensus. *Neonatal Network, 5*(6), 7–16.

Penticuff, J. H. (1988). Neonatal intensive care: Parental prerogatives. *Journal of Perinatal and Neonatal Nursing, 1*(3), 77–86.

Penticuff, J. H. (1995). Nursing ethics in perinatal care. In A. Goldworth, W. Silverman, D. K. Stevenson, E. W. D. Young, & R. Rivers (Eds.), *Ethics and perinatology*. New York, NY: Oxford University Press.

Penticuff, J. H. (1998). Defining futility in neonatal intensive care. *Nursing Clinics of North America, 33*(2), 339–352.

Pinch, W. J., & Spielman, M. L. (1993). Parental perceptions of ethical issues post-NICU discharge. *Western Journal of Nursing Research, 15*(4), 422–440. doi:10.1177/019394599301500403

Pinch, W. J., & Spielman, M. L. (1996). Ethics in the neonatal intensive care unit: Parental perceptions at 4 years postdischarge. *Advances in Nursing Science, 19*(1), 72–85. doi:10.1097/00012272-199609000-00008

Pinkerton, J. V., Finnerty, J. J., Lombardo, P. A., Rorty, M. V., Chapple, H., & Boyle, R. J. (1997). Parental rights at the birth of a near-viable infant: Conflicting perspectives. *American Journal of Obstetrics and Gynecology, 177*(2), 283–288. doi:10.1016/S0002-9378(97)70188-1

President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. (1983). *Deciding to forego life-sustaining treatment*. Washington, DC: U.S. Government Printing Office.

Raines, D. A. (1996). Parents' values: A missing link in the neonatal intensive care equation. *Neonatal Network, 15*(3), 7–12.

Rogers, S., Babgi, A., & Gomez, C. (2008). Educational interventions in end-of-life care: Part I: An education intervention responding to moral distress of NICU nurses provided by an ethics consultation team. *Advances in Neonatal Care, 8*(1), 56–65. doi:10.1097/01.ANC.0000311017.02005.20

Rushton, C. H. (2000). Pediatric palliative care: Coming of age (online journal). *Innovations in End-of-Life Care, 2*(2). https://www.caringcommunity.org/helpful-resources/models-research/innovations-in-end-of-life-care-journal/

Sanchez-Reilly, S., Morrison, S., Carey, E., Bernacki, R., O'Neil, L., Kapo, J., . . . Thomas, J. L. (2013). Caring for oneself to care for others: Physicians and their self-care. *Journal of Supportive Oncology, 11*(2), 75–81.

Sharp, C. (1991). Use of chaplaincy in the neonatal intensive care unit. *Southern Medical Journal, 84*(12), 1482–1486.

Stephenson, J. (2000). Palliative and hospice care needed for children with life-threatening conditions. *Journal of the American Medical Association, 284*(19), 2437–2438. doi:10.1001/jama.284.19.2437

Stinson, R., & Stinson, P. (1979). *The long dying of baby Andrew.* Boston, MA: Little, Brown.

Tan, J. S., Docherty, S. L., Barfield, R., & Brandon, D. H. (2012). Addressing parental bereavement support needs at the end of life for infants with complex chronic conditions. *Journal of Palliative Medicine, 15*(5), 579–584. doi:10.1089/jpm.2011.0357

Thaxton, C., Carter, B., & Dang Hornig, C. (2016). Palliative care in the neonatal intensive care unit. In B. R. Ferrell, N. Coyle, & J. Paice (Eds.), *Oxford textbook of palliative nursing* (4th ed., pp. 909–924). Oxford, NY: Oxford University Press. doi:10.1093/med/9780199332342.001.0001

Wallerstedt, C., & Higgins, P. (1996). Facilitating perinatal grieving between the mother and the father. *Journal of Obstretic, Gynecology & Neonatal Nursing, 25*(5), 389–394. doi:10.1111/j.1552-6909.1996.tb02442.x

Weir, R. F. (1984). *Selective nontreatment of handicapped newborns*. New York, NY: Oxford University Press.

Weir, R. F. (1995). Withholding and withdrawing therapy and actively hastening death II. In A. Goldworth, W. Silverman, D. K. Stevenson, E. W. D. Young, & R. Rivers (Eds.), *Ethics and perinatology*. New York, NY: Oxford University Press.

Wolfe, J. (2000). Suffering in children at the end of life: Recognizing an ethical duty to palliate. *Journal of Clinical Ethics, 11*(2), 157–161.

Wolfe, J., Grier, H. E., Klar, N., Levin, S. B., Ellenbogen, J. M., Salem-Schatz, S., . . . Weeks, J. C. (2000). Symptoms and suffering at the end of life in children with cancer. *New England Journal of Medicine, 342*(5), 326–333. doi:10.1056/NEJM200002033420506

Wool, C., & Northam, S. (2011). The Perinatal Palliative Care Perceptions and Barriers Scale Instrument©: Development and validation. *Advances in Neonatal Care, 11*(6), 397–403. doi:10.1097/ANC.0b013e318233809a

World Health Organization. (2014). *Global atlas of palliative care at the end of life*. Geneva, Switzerland: World Wide Palliative Care Alliance/World Health Organization.

Yellin, P. B., Levin, B. W., Krantz, D. H., Shinn, M., Driscoll, J. M., & Fleischman, A. R. (1998). Neonatologists' decisions about withholding and withdrawing treatments from critically ill newborns. *Pediatrics, 102*(3), 757.

CHAPTER 37

Postdischarge Care of the Newborn, Infant, and Families

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INTRODUCTION

The multiple problems that bring an infant to a neonatal intensive care unit (NICU) have been described, in depth, throughout the preceding chapters. Upon hospital discharge, high-risk infants require no less care than in the hospital as the healthcare needs of the initially sick infant often remain numerous and complex. Postdischarge and follow-up care focuses on the convalescing infant's growth, development, health promotion, disease prevention, chronic disease management, and care coordination. Importantly, parents also need care after the infant's hospital discharge. The transition from hospital to home for infants and their families is a very important and crucial period. This transition starts when the family begins to accept the role of the full-time caregiver outside the safety net of the hospital. The focus of this chapter is on the infant and parental care after hospital discharge.

POSTDISCHARGE CARE FOR HIGH-RISK INFANTS

The American Academy of Pediatrics (AAP) and the American College of Obstetricians and Gynecologists (ACOG) recommend healthcare professionals to give special considerations to the four following groups of high-risk newborn infants before discharge: (a) preterm infant, (b) infant with special healthcare needs or dependence on technology, (c) infant at risk because of family issues, and (d) infant with anticipated early death (AAP & ACOG, 2017). Discharge criteria as well as the postdischarge care depend on the different needs of these patient categories. In general, for high-risk infants to be discharged, they have to be physiologically stable; the decision is based on the clinical judgment of health professionals and determination of the infant's medical status.

The first category, preterm infants, can be discharged when oral feedings are sufficient to support appropriate growth. Also, preterm infants can be discharged when they are able to maintain normal body temperature in a homelike environment without supplemental heat and when sufficient mature respiratory control is present (AAP Committee on Fetus and Newborn, 2008). Most preterm infants achieve major physiological milestones by 36 to 37 weeks' postmenstrual age (AAP & ACOG, 2017), but feeding and oxygen milestones are often achieved last (Bakewell-Sachs, Medoff-Cooper, Escobar, Silber, & Lorch, 2009). Apneic episodes are common in preterm infants before discharge; feedings and weight gain are also challenging issues (Briere, McGrath, Cong, & Cusson, 2014; Eichenwald et al., 2016; Ross & Browne, 2013). Thus, observation (up to 7 days without apnea) and stable pattern in feeding/gaining weight before discharge from an NICU is recommended (Eichenwald et al., 2016); readiness in these physiological skills will depend on the gestational age (Lorch, Srinivasan, & Escobar, 2011).

For NICU infants before discharge, weight gain of 15 to 30 g/day must continue over a reasonable time (several days to 1 week); milk fortification, iron, vitamins, foliate, and vitamin D supplementation are often necessary (LaHood & Bryant, 2007; Teller, Embleton, Griffin, & van Elburg, 2016); and weight gain should occur in an open environment (crib). This gain should continue during the first 3 to 4 months of life and then decline to 5 to 15 g/day by the age of 12 to 18 months (Sherman, Lauriello, & Aylward, 2016). For larger and healthier infants, 108 kcal/kg/day can be sufficient for adequate growth. For preterm infants, 110 to 130 kcal/kg/day can be required with increased protein (Shakeel, 2016; Sherman et al., 2016). There is a need to avoid excessive weight gain, which may result in health problems such as obesity, hypertension, and cardiovascular disease (Casey, 2008; Sherman et al., 2016). Nutritional requirements vary depending on the infant's past medical problems, status, and tolerance of feedings; thus, individualized postdischarge instructions are necessary. Available and widely used growth charts are not always valid for preterm infants or infants with continuing health problems, but some recent information is available for infants of different gestational ages (Villar et al., 2014). Length, head circumference, and weight should always be considered together, and nutritional assessment of the infant is more than just body measurements and may even require indirect calorimetry (Sherman et al., 2016). In general, frontal-to-occipital head circumference in preterm infants should be 0.7 to 1 cm/week (in term infants 0.5 cm) in the immediate postnatal period; by 12 to 18 months of age, it should decline to 0.1 to 0.4 cm/month (Sherman et al., 2016). Increase in crown-to-heel length should be approximately 0.8 to 1.1 cm/week in preterm infants (0.7–0.75 in term babies), and by 12 to 18 months of age, it should decline to 0.75 to 1.5 cm/month (Sherman et al., 2016). Consultation with a pediatric dietitian or an infant nutrition specialist should be obtained if there are concerns about growth failure and catch-up (Peters & Pompeii-Wolfe, 2018) as the adherence to the nutrition guidelines can be low

(Francis et al., 2018). Additional information on specific formulas, nutrition aspects, and standardized growth charts are presented in Chapter 20, Nutrition Management of Premature Infants, of this book.

In the second category, the infant with special healthcare needs or dependence on technology will have differing needs than the average NICU graduate. Depending on the exact health condition (chronic lung disease [CLD], genetic condition, congenital heart disease [CHD], and postsurgical and late preterm infants), the infant may require more calories due to the "work of breathing" such as in a case with CLD or CHD. With CLD, the infant may require 120 to 150 kcal/kg/day plus increased protein intake, fluid restriction, electrolyte management, and control of vital functions (Sherman et al., 2016). An infant with CLD will often require home oxygen therapy, so appropriate parental teaching should be done before discharge. A pediatric pulmonologist should also be involved in postdischarge management of such patients; periodic evaluation of electrolyte status should also be performed due to the use of diuretics in such infants. An infant with cardiac disease will also often require fluid restriction and may need increased caloric intake as well. A pediatric cardiologist should be involved in postdischarge management of such infants; periodic evaluation of electrolyte status also should be performed due to the use of diuretics in such infants.

The third category of infants who should receive attention before and after discharge are infants who are at health risk because of family issues. The infant may or may not be premature, or having specific health needs, but the family may have problems in adjusting to having a once sick infant at home who now is ready for discharge (discussed later in this chapter). For infants in the fourth category—infants with anticipated early death—the aspects of the care are described in Chapter 36, Palliative and End-of-Life Care.

Follow-Up of High-Risk Infants

Careful attention should be given to any NICU graduate. Since 1936, the attention was given to taking preterm infants home (Lundeen, 1937). The follow-up appointments with primary care providers for high-risk infants should occur in accordance with the needs of the patient (AAP & ACOG, 2017). For preterm infants (including late preterm) and infants with early discharge from the maternity unit (<48 hours after delivery), AAP and ACOG (2017) recommend that the first appointment with the primary caregiver should occur in the first 24 to 48 hours after discharge. In the immediate period after discharge, some of the high-risk infants should be examined weekly or semimonthly (AAP & ACOG, 2017). Neurodevelopmental, behavioral, and sensory status should be assessed more than once during the first year "to ensure early identification of problems and referral for the appropriate interventions" (AAP & ACOG, 2017, p. 471). Infants born with birth weight less than 1,500 g, as well as infants with hypoxic–ischemic encephalopathy (HIE), seizures, hypoxic cardiorespiratory failure, and multiple congenital anomalies, should have standard neurodevelopmental tests at 1 and 2 years of corrected age (AAP & ACOG, 2017). Infants who underwent major and minor surgeries (e.g., diaphragmatic hernia, major heart defects, pyloric stenosis, inguinal hernia) have been shown to have some degree of developmental delays (Walker, Holland, Halliday, & Badawi, 2012). Several risk factors can be identified for developmental delays in surgical patients: genetic predisposition, prematurity, premorbid status, age at the time of surgery, duration of the procedure, and type of anesthetic/analgesic agents used (Walker et al., 2012). Purdy and Melwak (2012) have also suggested the following "red flags" when thorough high-risk infant follow-up care is required:

- Low Apgar score at 5 minutes (<4)
- Intraventricular hemorrhage more than Grade II, hydrocephalus
- HIE, abnormal neurological examination (tremors, hypotonia/hypertonia), seizures
- Hyperbilirubinemia close to exchange transfusion levels
- Severe infections (sepsis, meningitis)
- Hypoglycemia requiring treatment
- Persistent pulmonary hypertension, extracorporeal membrane oxygenation, and use of inhaled nitric oxide
- Discharge on apnea monitor and caffeine
- Infant of substance-abusing mother
- Congenital birth defects (such as Trisomy 21 or Down's syndrome; Purdy & Melwak, 2012)

Frequency of follow-up visits for the *well infant* varies with local and community practices as well as with the patient (AAP & ACOG, 2017); however, it should be consistent with AAP's guidelines on preventive pediatric healthcare. *The Bright Futures* online resource provides guidance, tools, and schedules for promoting health in the neonatal and pediatric populations (for resource, see https://brightfutures.aap.org/Pages/default.aspx). The follow-up visit can take place at home or clinic; physical examination and measurements, developmental surveillance, psychosocial, and behavioral assessments are recommended at the infancy period at 1, 2, 4, 6, and 9 months of age. In early childhood, these visits should take place at 12, 15, 18, 24, and 30 months of age and then at 3 and 4 years of age. Developmental screening is recommended at 9, 18, and 30 months of age (AAP, 2019; Figure 37.1). However, high-risk infants might require additional health checkups; thus, every infant should be managed on the individual basis.

Due to risks of visual impairments in NICU patients (i.e., retinopathy of prematurity, ROP), ophthalmic examinations should be performed. Infants less than or equal to 1,500 g or less than or equal to 32 weeks, infants with unstable clinical course, should have retinal screening (starting at the hospital usually). The first fundal examination in infants above 22 weeks of gestation should occur at 31 weeks' postmenstrual age or between 4 and 9 weeks of chronological age, depending on the gestational age at birth; follow-up appointments should occur in 1- to 3-week intervals depending on the initial fundal examination (Fierson, AAP Section on Ophthalmology, American Academy of Ophthalmology, American Association for Pediatric Ophthalmology and Strabismus, & American Association of Certified Orthoptists, 2018). It had also been recommended that preterm infants with or without ROP should be evaluated at 4 to 6 months of age and then yearly (Fierson, AAP Section on Ophthalmology, American Academy of Ophthalmology, American Association for Pediatric Ophthalmology and Strabismus, & American Association of Certified Orthoptists, 2018). Special attention should be given to parents of preterm infants with low health literacy and limited English language proficiency: These parents often lack knowledge about ROP (Eneriz-Wiemer et al., 2018).

Hearing screening is also vitally important as hearing-impaired children suffer irreversible delays in speech and language development; all infants should be screened regardless of the risk (Delaney, 2018). Permanent hearing loss remains a serious complication of prematurity, certain neonatal diseases, or prolonged oxygen and antibiotics' use (Delaney, 2018). Hearing screening should be performed before discharge in any infant who was hospitalized for more than 5 days; auditory brainstem response (ABR), otoacoustic emissions (OAEs), and automated ABR (AABR) are the widely used methods for newborn hearing screening; ABR and auditory steady-state response testing (ASSR) can be especially helpful to obtain specific information about specifics of infant

hearing loss (Delaney, 2018). After discharge, an infant should be evaluated at 1 and 3 months of age; infants with identified hearing loss should be enrolled in early intervention (EI) programs by 6 months of age (AAP Early Hearing Detection and Intervention, 2018). Very early screening (by 1 month of age), diagnosis in the first 3 months, and enrollment into EI services are beneficial for infants with hearing loss in terms of language development (AAP Early Hearing Detection and Intervention, 2018). Many states also recommend that at-risk children should be evaluated by an audiologist every 6 months for the first 3 years of life (Delaney, 2018). Healthcare professionals at follow-up clinics, EI programs, and primary care settings should pay careful attention to NICU patients in terms of hearing—only 61% of NICU graduates with permanent hearing loss were enrolled in EI programs in 2012 (Williams, Alam, & Gaffney, 2015). Special attention should be given to low educational level of the families: One study showed that only one third of infants were screened and followed up within the recommended time frame (Holte et al., 2012) and found that there are certain misunderstandings, misconceptions, and myths in parents regarding hearing loss in infants (Delaney, 2018). The AAP (2018a) Program to Enhance the Development of Infants and Children (PEHDIC) developed 1-3-6 guidelines for pediatric medical home providers: screening by 1 month of age, diagnosis of hearing loss by 3 months of age, and entry into EI services by 6 months of age. This guideline can be found at www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/PEHDIC/Documents/Algorithm1_2010.pdf (see Figure 37.2). According to AAP (2018a), only 86.9% of infants receive hearing re-screening before 1 month of age; only 69.1% of infants who do not pass a hearing screening test are diagnosed with hearing loss before 3 months of age; of those who are diagnosed, only 67% receive intervention before 6 months of age; and almost 36% of infants who do not pass a newborn hearing test are lost to follow-up (AAP, 2018a). Although early screening and EI are vital (Vohr, 2016), wide variations in tests used for infants as well as differences in waiting times (up to 5 months), loss to follow-up, and limited referral to EI were reported (C. L. Liu, Farrell, MacNeil, Stone, & Barfield, 2008; Munoz, Nelson, Goldgewicht, & Odell, 2011; Wang, Elliott, McGlynn, Brook, & Schuster, 2008).

Immunizations

Appropriate immunizations should be given at discharge from a hospital (AAP, 2019). The full schedule can be found at https://redbook.solutions.aap.org/selfserve/ssPage.aspx?SelfServeContentId=Immunization_Schedules. Vaccinations for preterm infants should be given according to the chronological age; routine immunization schedules are not changed. Some specifics related to the hepatitis B (HepB) immunizations in infants weighing less than 2,000 g are as follows: The first HepB vaccine is given at 1 month of age or at discharge and then four vaccines are given at 1, 2, and 6 (up to 18) months of age (AAP, 2019). AAP (2019) recommends adding HepB immunoglobulin to HepB vaccine in infants of mothers with unknown HBsAg status. In infants who are heavier than 2,000 g and those mothers who are HBsAg positive, immunoglobulin should be added to HepB vaccine, but no later than 1 week after birth (AAP, 2019).

Vaccinations can be delayed if needed (i.e., due to the present medical conditions, transient illnesses, and rehospitalizations). Careful attention should be given to the immunization schedule of NICU graduates: One study reported that only 51% of NICU infants were given routine immunizations and 27% of infants had no vaccines at all (Navar-Boggan, Halsey, Escobar, Golden, & Klein, 2011). The schedule for the recommended vaccinations and catch-up schedule for patients who start late, or more than 1 month behind, can be found at the Red Book online resource mentioned previously (AAP, 2018a, 2019). Please see some recommended schedules for immunization in Figure 37.3.

To prevent respiratory infection, specifically respiratory syncytial virus (RSV) infection, a monoclonal antibody (palivizumab or Synagis by AstraZeneca Pharmaceuticals, Wilmington, DE) can be administered to preterm infants born before 29 weeks' gestation. A proper use and adequate number of doses are of vital importance. RSV immunizations range from one dose to five monthly doses (intramuscularly, 15 mg/kg/dose). Palivizumab can be given at 48 to 72 hours before discharge or as soon as possible after discharge, preferably 1 month before RSV season. During RSV season in North America (November to March, sometimes April), fewer doses may be required (AAP & ACOG, 2017). Infants with CLD or CHD who are younger than 12 months of age and on the medical therapy, as well as preterm infants born before 29 completed weeks of gestation, are eligible for maximum five monthly doses (AAP, 2014). For preterm infants with CLD or CHD, immunizations usually start on November 1 for most geographic locations of the United States. For Florida and Alaska timing for vaccination may vary due to different in the length of RSV season. Adequate coverage of the infants eligible for the RSV vaccination can be a problem: One French study reported that only 77% of infants received complete prophylaxis (Torchin et al., 2018). For preterm infants without CLD, the detailed dosage and timing can be found at the Red Book online resource (AAP, 2019). Importantly, RSV seasons may vary from country to country and region to region; the reference to appropriate professional guidelines should be made.

Early Intervention Services

EI services and programs aim to prevent or improve cognitive, behavioral, developmental, and physical outcomes in infants and preschoolers; these services also provide family support and decrease parental stress, improving mother–infant interactions and feeding practices, and having positive effects on both maternal and infant outcomes (Borghini et al., 2014; Fontana et al., 2018; Litt, Glymour, Hauser-Cram, Hehir, & McCormick, 2018; Rose, Herzig, & Hussey-Gardner, 2014; Spittle, Anderson, Boyd, & Doyle, 2015; Spittle & Treyvaud, 2016; Zhang, Kurtz, Lee, & Liu, 2014). In the United States, EI service is covered under the Individuals with Disabilities Education Act (IDEA), Part C, and infants are eligible to participate (U.S. Department of Education, 2011). However, these programs are expensive, and referral to them can be problematic. Nationally, EI services cost an estimated $611 million (Behrman & Butler, 2007); special education services associated with a higher prevalence of four disabling conditions (such as cerebral palsy [CP], mental retardation, vision impairment, and hearing loss) add $1.1 billion or $2,200 per preterm infant (Behrman & Butler, 2007). In Massachusetts, the program costs were estimated to be about $66 million in 2003 with a mean cost of $857 per infant involved in EI; however, for infants whose gestational age was 24 to 31 weeks, the costs were over $5,000, and for 32 to 36 weeks' gestation, they were $1,578 (Clements, Barfield, Ayadi, & Wilber, 2007). Additionally, criteria for these programs vary by state, and not all high-risk infants and their families are ever referred (Little, Kamholz, Corwin, Barrero-Castillero, & Wang, 2015; Tang, Feldman, Huffman, Kagawa, & Gould, 2012). Tang et al. (2012) found that 34% of infants who had high-risk conditions were not referred, even though they were eligible for EI programs. Other disparities in EI referral practices have also been documented: Referral was more likely in multiple-birth infants and less likely in infants more than 28 weeks of gestation, infants of non-Hispanic black mothers and mothers without private

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN®

Recommendations for Preventive Pediatric Health Care

Bright Futures/American Academy of Pediatrics

Bright Futures
prevention and health promotion for infants, children, adolescents, and their families™

Each child and family is unique; therefore, these Recommendations for Preventive Pediatric Health Care are designed for the care of children who are receiving competent parenting, have no manifestations of any important health problems, and are growing and developing in a satisfactory fashion. Developmental, psychosocial, and chronic disease issues for children and adolescents may require frequent counseling and treatment visits separate from preventive care visits. Additional visits also may become necessary if circumstances suggest variations from normal.

These recommendations represent a consensus by the American Academy of Pediatrics (AAP) and Bright Futures. The AAP continues to emphasize the great importance of continuity of care in comprehensive health supervision and the need to avoid fragmentation of care.

Refer to the specific guidance by age as listed in the Bright Futures Guidelines (Hagan JF, Shaw JS, Duncan PM, eds.Bright Futures: Guidelines for Health Supervision of Infants, Children, and Adolescents. 4th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2017).

The recommendations in this statement do not indicate an exclusive course of treatment or standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

	INFANCY							EARLY CHILDHOOD							MIDDLE CHILDHOOD						ADOLESCENCE										
AGE[1]	Prenatal[2]	Newborn[3]	3-5 d[4]	By 1 mo	2 mo	4 mo	6 mo	9 mo	12 mo	15 mo	18 mo	24 mo	30 mo	3 y	4 y	5 y	6 y	7 y	8 y	9 y	10 y	11 y	12 y	13 y	14 y	15 y	16 y	17 y	18 y	19 y	20 y	21 y
HISTORY Initial/Interval	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
MEASUREMENTS																															
Length/Height and Weight		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Head Circumference		●	●	●	●	●	●	●	●	●	●	●																			
Weight for Length		●	●	●	●	●	●	●	●	●	●																				
Body Mass Index[5]												●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Blood Pressure[6]		★	★	★	★	★	★	★	★	★	★	★	★	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
SENSORY SCREENING																															
Vision[7]		★	★	★	★	★	★	★	★	★	★	★	★	●	●	●	●	★	●	★	●	★	●	★	★	●	★	★	★	★	★
Hearing		●[8]	●[9] →	→	★	★	★	★	★	★	★	★	★	★	●	●	●	★	●	★	●	←	●	●	[10] →	←	●	→	←	●	→	
DEVELOPMENTAL/BEHAVIORAL HEALTH																															
Developmental Screening[11]								●			●		●																		
Autism Spectrum Disorder Screening[12]											●	●																			
Developmental Surveillance		●	●	●	●	●	●		●	●		●		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Psychosocial/Behavioral Assessment[13]		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Tobacco, Alcohol, or Drug Use Assessment[14]																						★	★	★	★	★	★	★	★	★	★
Depression Screening[15]																							●	●	●	●	●	●	●	●	●
Maternal Depression Screening[16]				●	●	●	●																								
PHYSICAL EXAMINATION[17]		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
PROCEDURES[18]																															
Newborn Blood		●[19]	●[20] →	→																											
Newborn Bilirubin[21]		●																													
Critical Congenital Heart Defect[22]		●																													
Immunization[23]		●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Anemia[24]						★			●	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★
Lead[25]							★	★	● or ★[26]		★	● or ★[26]		★	★	★	★															
Tuberculosis[27]				★			★		★			★		★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★
Dyslipidemia[28]												★			★		★		★	←	● →	→	★	★	★	★	★	←	● →			
Sexually Transmitted Infections[29]																						★	★	★	★	★	★	★	★	★	★
HIV[30]																						★	★	★	★	←	● →		★	★	★
Cervical Dysplasia[31]																															●
ORAL HEALTH[32]							●[33]	●[33]	★		★	★	★	★	★	★	★														
Fluoride Varnish[34]							←	←	←	● →	→	→	→	→	→	→																
Fluoride Supplementation[35]							★	★	★		★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★	★				
ANTICIPATORY GUIDANCE	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●

1. If a child comes under care for the first time at any point on the schedule, or if any items are not accomplished at the suggested age, the schedule should be brought up-to-date at the earliest possible time.
2. A prenatal visit is recommended for parents who are at high risk, for first-time parents, and for those who request a conference. The prenatal visit should include anticipatory guidance, pertinent medical history, and a discussion of benefits of breastfeeding and planned method of feeding, per "The Prenatal Visit" (http://pediatrics.aappublications.org/content/124/4/1227.full).
3. Newborns should have an evaluation after birth, and breastfeeding should be encouraged (and instruction and support should be offered).
4. Newborns should have an evaluation within 3 – 5 days of birth and within 48 – 72 hours after discharge from the hospital to include evaluation for feeding and jaundice. Breastfeeding newborns should receive formal breastfeeding evaluation, and their mothers should receive encouragement and instruction, as recommended in "Breastfeeding and the Use of Human Milk" (http://pediatrics.aappublications.org/content/129/3/e827.full). Newborns discharged less than 48 hours after delivery must be examined within 48 hours of discharge, per "Hospital Stay for Healthy Term Newborns" (http://pediatrics.aappublications.org/content/125/2/405.full).
5. Screen, per "Expert Committee Recommendations Regarding the Prevention, Assessment, and Treatment of Child and Adolescent Overweight and Obesity: Summary Report" (http://pediatrics.aappublications.org/content/120/Supplement_4/S164.full).
6. Blood pressure measurement in infants and children with specific risk conditions should be performed at visits before age 3 years.
7. A visual acuity screen is recommended at ages 4 and 5 years, as well as in cooperative 3-year-olds. Instrument-based screening may be used to assess risk at ages 12 and 24 months, in addition to the well visits at 3 through 5 years of age. See "Visual System Assessment in Infants, Children, and Young Adults by Pediatricians" (http://pediatrics.aappublications.org/content/137/1/e20153596) and "Procedures for the Evaluation of the Visual System by Pediatricians" (http://pediatrics.aappublications.org/content/137/1/e20153597).
8. Confirm initial screen was completed, verify results, and follow up, as appropriate. Newborns should be screened per "Year 2007 Position Statement: Principles and Guidelines for Early Hearing Detection and Intervention Programs" (http://pediatrics.aappublications.org/content/120/4/898.full).
9. Verify results as soon as possible, and follow up, as appropriate.
10. Screen with audiometry including 6,000 and 8,000 Hz high frequencies once between the ages of 11 and 14 years, once between the ages of 15 and 17 years, and once between the ages of 18 and 21 years. See "The Sensitivity of Adolescent Hearing Screens Significantly Improves by Adding High Frequencies" (http://www.jahonline.org/article/S1054-139X(16)00048-3/fulltext).
11. See "Identifying Infants and Young Children With Developmental Disorders in the Medical Home: An Algorithm for Developmental Surveillance and Screening" (http://pediatrics.aappublications.org/content/118/1/405.full).
12. Screening should occur per "Identification and Evaluation of Children With Autism Spectrum Disorders" (http://pediatrics.aappublications.org/content/120/5/1183.full).
13. This assessment should be family centered and may include an assessment of child social–emotional health, caregiver depression, and social determinants of health. See "Promoting Optimal Development: Screening for Behavioral and Emotional Problems" (http://pediatrics.aappublications.org/content/135/2/384) and "Poverty and Child Health in the United States" (http://pediatrics.aappublications.org/content/137/4/e20160339).
14. A recommended assessment tool is available at http://www.ceasar-boston.org/CRAFFT/index.php.
15. Recommended screening using the Patient Health Questionnaire (PHQ)-2 or other tools available in the GLAD-PC toolkit and at http://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/Mental-Health/Documents/MH_ScreeningChart.pdf.
16. Screening should occur per "Incorporating Recognition and Management of Perinatal and Postpartum Depression Into Pediatric Practice" (http://pediatrics.aappublications.org/content/126/5/1032).
17. At each visit, age-appropriate physical examination is essential, with infant totally unclothed and older children undressed and suitably draped. See "Use of Chaperones During the Physical Examination of the Pediatric Patient" (http://pediatrics.aappublications.org/content/127/5/991.full).
18. These may be modified, depending on entry point into schedule and individual need.

(continued)

KEY: ● = to be performed ★ = risk assessment to be performed with appropriate action to follow, if positive ← ● → = range during which a service may be provided

FIGURE 37.1 American Academy of Pediatrics recommendations for well-child follow-up care appointments.

Source: With permission, from the American Academy of Pediatrics. (2019). *Recommendations for preventive pediatric health care.* Retrieved from https://www.aap.org/en-us/Documents/periodicity_schedule.pdf

(continued)

19. Confirm initial screen was accomplished, verify results, and follow up, as appropriate. The Recommended Uniform Newborn Screening Panel (https://hrsa.gov/advisory-committees/heritable-disorders/rusp/index.html), as determined by The Secretary's Advisory Committee on Heritable Disorders in Newborns and Children, and state newborn screening laws/regulations (http://genes-r-us.uthscsa.edu/home) establish the criteria for and coverage of newborn screening procedures and programs.
20. Verify results as soon as possible, and follow up, as appropriate.
21. Confirm initial screening was accomplished, verify results, and follow up, as appropriate. See "Hyperbilirubinemia in the Newborn Infant ≥35 Weeks' Gestation: An Update With Clarifications" (http://pediatrics.aappublications.org/content/124/4/1193).
22. Screening for critical congenital heart disease using pulse oximetry should be performed in newborns, after 24 hours of age, before discharge from the hospital, per "Endorsement of Health and Human Services Recommendation for Pulse Oximetry Screening for Critical Congenital Heart Disease"(http://pediatrics.aappublications.org/content/129/1/190.full).
23. Schedules, per the AAP Committee on Infectious Diseases, are available at http://redbook.solutions.aap.org/SS/Immunization_Schedules.aspx.Every visit should be an opportunity to update and complete a child's immunizations.
24. See "Diagnosis and Prevention of Iron Deficiency and Iron-Deficiency Anemia in Infants and Young Children (0–3 Years of Age)" (http://pediatrics.aappublications.org/content/126/5/1040.full).
25. For children at risk of lead exposure, see "Low Level Lead Exposure Harms Children: A Renewed Call for Primary Prevention" (http://www.cdc.gov/nceh/lead/ACCLPP/Final_Document_030712.pdf).
26. Perform risk assessments or screenings as appropriate, based on universal screening requirements for patients with Medicaid or in high prevalence areas.
27. Tuberculosis testing per recommendations of the AAP Committee on Infectious Diseases, published in the current edition of the AAP *Red Book: Report of the Committee on Infectious Diseases.*Testing should be performed on recognition of high-risk factors.
28. See "Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents"(https://www.nhlbi.nih.gov/health-topics/integrated-guidelines-for-cardiovascular-health-and-risk-reduction-in-children-and-adolescents).
29. Adolescents should be screened for sexually transmitted infections (STIs) per recommendations in the current edition of the AAP Red Book: Report of the Committee on Infectious Diseases.
30. Adolescents should be screened for HIV according to the USPSTF recommendations (http://www.uspreventiveservicestaskforce.org/uspstf/uspshivi.htm) once between the ages of 15 and 18, making every effort to preserve confidentiality of the adolescent. Those at increased risk of HIV infection, including those who are sexually active, participate in injection drug use, or are being tested for other STIs, should be tested for HIV and reassessed annually.
31. See USPSTF recommendations (http://www.uspreventiveservicestaskforce.org/uspstf/uspscerv.htm). Indications for pelvic examinations prior to age 21 are noted in "Gynecologic Examination for Adolescents in the Pediatric Office Setting" (http://pediatrics.aappublications.org/content/126/3/583.full).
32. Assess whether the child has a dental home. If no dental home is identified, perform a risk assessment (https://www.aap.org/RiskAssessmentTool) and refer to a dental home. Recommend brushing with fluoride toothpaste in the proper dosage for age. See "Maintaining and Improving the Oral Health of Young Children" (http://pediatrics.aappublications.org/content/134/6/1224).
33. Perform a risk assessment (https://www.aap.org/RiskAssessmentTool). See "Maintaining and Improving the Oral Health of Young Children" (http://pediatrics.aappublications.org/content/134/6/1224).
34. See USPSTF recommendations (http://www.uspreventiveservicestaskforce.org/uspstf/uspsdnch.htm). Once teeth are present, fluoride varnish may be applied to all children every 3–6 months in the primary care or dental office. Indications for fluoride use are noted in "Fluoride Use in Caries Prevention in the Primary Care Setting"(http://pediatrics.aappublications.org/content/134/3/626).
35. If primary water source is deficient in fluoride, consider oral fluoride supplementation. See"Fluoride Use in Caries Prevention in the Primary Care Setting" (http://pediatrics.aappublications.org/content/134/3/626).

Summary of Changes Made to the Bright Futures/AAP Recommendations for Preventive Pediatric Health Care
(Periodicity Schedule)

This schedule reflects changes approved in February 2017 and published in April 2017.
For updates, visit www.aap.org/periodicityschedule.
For further information, see the *Bright Futures Guidelines* , 4th Edition, *Evidence and Rationale chapter* (https://brightfutures.aap.org/Bright%20Futures%20Documents/BF4_Evidence_Rationale.pdf).

CHANGES MADE IN FEBRUARY 2017

HEARING
- Timing and follow-up of the screening recommendations for hearing during the infancy visits have been delineated. Adolescent risk assessment has changed to screening once during each time period.
- Footnote 8 has been updated to read as follows: "Confirm initial screen was completed, verify results, and follow up, as appropriate Newborns should be screened, per 'Year 2007 Position Statement: Principles and Guidelines for Early Hearing Detection and Intervention Programs' (http://pediatrics.aappublications.org/content/120/4/898.full)."
- Footnote 9 has been added to read as follows: "Verify results as soon as possible, and follow up, as appropriate."
- Footnote 10 has been added to read as follows: "Screen with audiometry including 6,000 and 8,000 Hz high frequencies once between 11 and 14 years, once between 15 and 17 years, and once between 18 and 21 years. See 'The Sensitivity of Adolescent Hearing Screens Significantly Improves by Adding High Frequencies' (http://www.jahonline.org/article/S1054-139X(16)00048-3/fulltext)."

PSYCHOSOCIAL/BEHAVIORAL ASSESSMENT
- Footnote 13 has been added to read as follows: "This assessment should be family centered and may include an assessment of child social–emotional health, caregiver depression, and social determinants of health. See 'Promoting Optimal Development: Screening for Behavioral and Emotional Problems' (http://pediatrics.aappublications.org/content/135/2/384) and 'Poverty and Child Health in the United States' (http://pediatrics.aappublications.org/content/137/4/e20160339)."

TOBACCO, ALCOHOL, OR DRUG USE ASSESSMENT
- The header was updated to be consistent with recommendations.

DEPRESSION SCREENING
- Adolescent depression screening begins routinely at 12 years of age (to be consistent with recommendations of the U.S. Preventive Services Task Force [USPSTF]).

MATERNAL DEPRESSION SCREENING
- Screening for maternal depression at 1-, 2-, 4-, and 6-month visits has been added.
- Footnote 16 was added to read as follows: "Screening should occur per 'Incorporating Recognition and Management of Perinatal and Postpartum Depression Into Pediatric Practice' (http://pediatrics.aappublications.org/content/126/5/1032)."

NEWBORN BLOOD
- Timing and follow-up of the newborn blood screening recommendations have been delineated.
- Footnote 19 has been updated to read as follows: "Confirm initial screen was accomplished, verify results, and follow up, as appropriate. The Recommended Uniform Newborn Screening Panel (http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/recommendedpanel/uniformscreeningpanel.pdf), as determined by The Secretary's Advisory Committee on Heritable Disorders in Newborns and Children, and state newborn screening laws/regulations (http://genes-r-us.uthscsa.edu/sites/genes-r-us/files/nbsdisorders.pdf) establish the criteria for and coverage of newborn screening procedures and programs."
- Footnote 20 has been added to read as follows: "Verify results as soon as possible, and follow up, as appropriate."

NEWBORN BILIRUBIN
- Screening for bilirubin concentration at the newborn visit has been added.
- Footnote 21 has been added to read as follows: "Confirm initial screening was accomplished, verify results, and follow up, as appropriate. See 'Hyperbilirubinemia in the Newborn Infant ≥35 Weeks' Gestation: An Update With Clarifications' (http://pediatrics.aappublications.org/content/124/4/1193)."

DYSLIPIDEMIA
- Screening for dyslipidemia has been updated to occur once between the ages of 9 and 11 years, and once between the ages of 17 and 21 years (to be consistent with guidelines of the National Heart, Lung, and Blood Institute).

SEXUALLY TRANSMITTED INFECTIONS
- Footnote 29 has been updated to read as follows: "Adolescents should be screened for sexually transmitted infections (STIs) per recommendations in the current edition of the AAP*Red Book: Report of the Committee on Infectious Diseases*".

HIV
- A subheading has been added for the HIV universal recommendation to avoid confusion with STIs selective screening recommendation.
- Screening for HIV has been updated to occur once between the ages of 15 and 18 years (to be consistent with recommendations of the USPSTF).
- Footnote 30 has been added to read as follows: "Adolescents should be screened for HIV according to the USPSTF recommendations (http://www.uspreventiveservicestaskforce.org/uspstf/uspshivi.htm) once between the ages of 15 and 18, making every effort to preserve confidentiality of the adolescent. Those at increased risk of HIV infection, including those who are sexually active, participate in injection drug use, or are being tested for other STIs, should be tested for HIV and reassessed annually."

ORAL HEALTH
- Assessing for a dental home has been updated to occur at the 12-month and 18-month through 6-year visits. A subheading has been added for fluoride supplementation, with a recommendation from the 6-month through 12-month and 18-month through 16-year visits.
- Footnote 32 has been updated to read as follows: "Assess whether the child has a dental home. If no dental home is identified, perform a risk assessment (https://www.aap.org/RiskAssessmentTool) and refer to a dental home. Recommend brushing with fluoride toothpaste in the proper dosage for age. See 'Maintaining and Improving the Oral Health of Young Children' (https://pediatrics.aappublications.org/content/134/6/1224)."
- Footnote 33 has been updated to read as follows: "Perform a risk assessment (https://www.aap.org/RiskAssessmentTool). See 'Maintaining and Improving the Oral Health of Young Children' (http://pediatrics.aappublications.org/content/134/6/1224)."
- Footnote 35 has been added to read as follows: "If primary water source is deficient in fluoride, consider oral fluoride supplementation. See 'Fluoride Use in Caries Prevention in the Primary Care Setting' (http://pediatrics.aappublications.org/content/134/3/626)."

FIGURE 37.1 (*continued*)

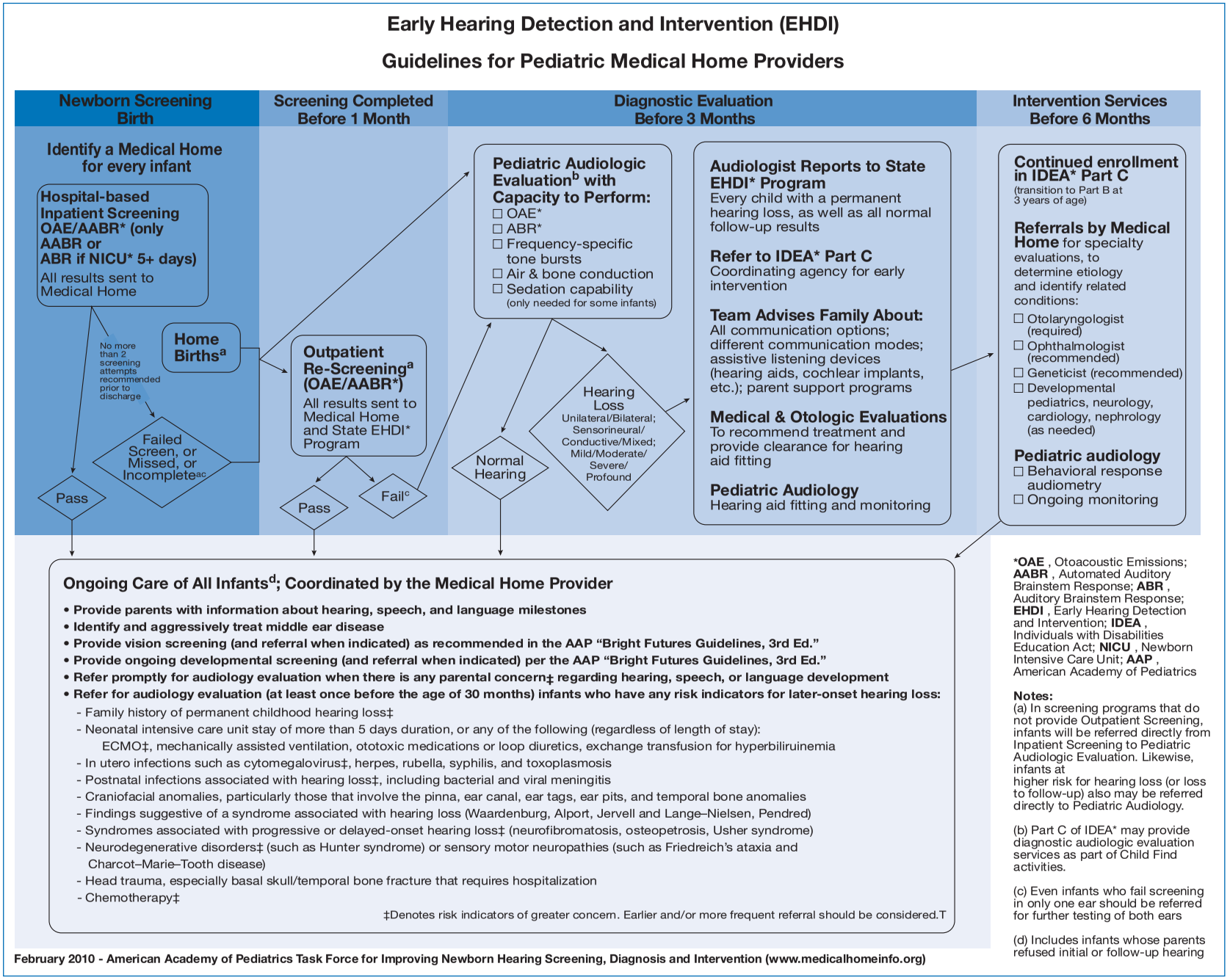

FIGURE 37.2 Early hearing detection and intervention (EHDI) guidelines for pediatric medical home providers.

Source: Adapted with permission from the American Academy of Pediatrics. (2010). *Early hearing detection and intervention (EHDI) guidelines for pediatric medical home providers.* Retrieved from https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/PEHDIC/Documents/Algorithm1_2010.pdf

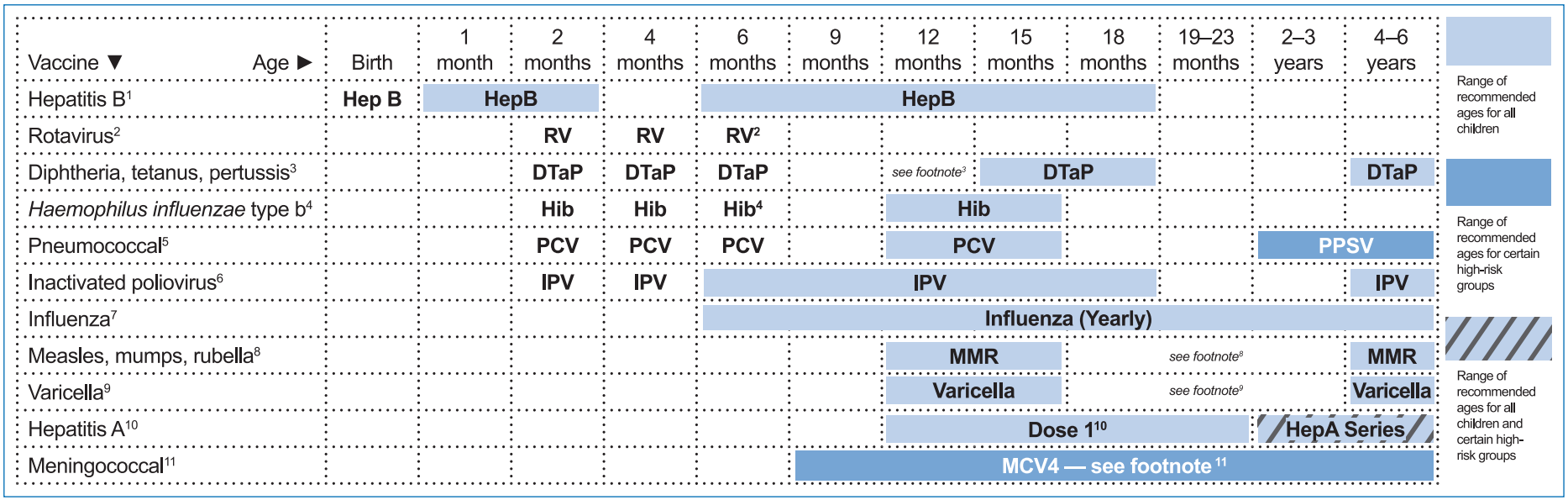

FIGURE 37.3 American Academy of Pediatrics immunization schedule, 2018.

Source: With permission from American Academy of Pediatrics. (2018b). Recommended childhood and adolescent immunization schedules: United States, 2018. *Pediatrics, 141*(3), e20180083. doi:10.1542/peds.2018-0083

insurance were also referred less than white mothers or those with insurance (Barfield et al., 2008). Regional variation in EI participation/utilization has been also shown to be significant: Services are less likely to be delivered in the South of the United States (Grant & Isakson, 2012). McManus, McCormick, Acevedo-Garcia, Ganz, and Hauser-Cram (2009) found that both child characteristics (poverty) and state program (strict or liberal eligibility criteria) influenced EI participation: Nonpoor children, those who lived in states with strict eligibility criteria, were nearly as likely as poor children who lived in states with liberal eligibility criteria to receive EI services (McManus et al., 2009). In this study, the overall rate of EI participation was 45.7%, ranging from 23.1% to 83.3% across the states.

Another important issue is that some health professionals do not feel prepared to assess the high-risk infant and their families; thus, referral may be inadequate because of insufficient knowledge and training of health professionals (Ballantyne et al., 2017; Brown & Smith, 2018; Browne & Talmi, 2012; G. Currie et al., 2018; Tregay et al., 2016). In Colorado, a statewide survey revealed that 77% of providers would like to have more education on infant evaluation, and 86% were interested in further education (Browne & Talmi, 2012). After implementing the collaborative educational programs where additional training and education were provided for health professionals involved in EI services (BABIES and Pre-STEPS), the referral rate and service provision increased from 33% to 52% over a 1-year initiative (Browne & Talmi, 2012). The Zero to Three National Center for Infants, Toddlers, and Families is another nonprofit organization that provides training and education to professionals and families (www.zerotothree.org).

Long-term measurable outcomes of EI programs are sometimes not precisely detectable through the years after NICU discharge, yet beneficial effects have been found in the most vulnerable children with complications (Spittle et al., 2015). Many high-risk infants are discharged with home oxygen, specific medications, and feeding tubes and may suffer long-term consequences of initial disease. In the United States, the estimated number of children with special healthcare needs (CSHCN) nationwide is 11,203,616 or 15.1% of the population; 14.8% of those have at least one unmet specific health need, and 23.4% have problems with getting referrals (National Survey of Children With Special Health Care Needs, 2009–2010, retrieved from www.childhealthdata.org). Thus, health professionals should carefully consider all the problems with provision of adequate postdischarge care and undertake appropriate actions to help NICU graduates, such as appropriate referral to specific treatments or EI services. Resources for information in EI services include the national Early Childhood Technical Assistance Center (ECTA; http://ectacenter.org/Default.asp).

One of the complications of newborn health issues is CP. The prevalence of CP at present is decreasing; even extremely low birth weight infants have only minor functional impairments (Johnson & Marlow, 2017). However, this is an important topic in postdischarge care that deserves attention from healthcare professionals. Over 1 billion people live with a disability, of which 200 million are children; more than 17 million people are living with a diagnosis of CP in the world (World Health Organization, 2011). CP is the most common physical disability of childhood, with one baby born with CP every 500 live births. The prevalence across the world varies with difficulty in obtaining accurate data from countries without data registries. Recently published Australian data report one of the few national decreases in the prevalence (and severity) of CP from 2–2.5 to 1.6–2 per 1,000 live births (Smithers-Sheedy et al., 2016).

In 2007, Rosenbaum and colleagues defined CP as a group of permanent disorders of the development of movement and posture, causing activity limitations that are attributed to nonprogressive disturbances that occurred in the developing fetal or infant brain (Rosenbaum et al., 2007). The motor disorders of CP are often accompanied by disturbances of sensation, perception, cognition, communication, and behavior; by epilepsy; and by secondary musculoskeletal problems (Rosenbaum et al., 2007). The injury to the brain in CP is static; however, accompanying impairments and comorbidities can be as disabling as the motor impairment and worsen over time (Novak, Hines, Goldsmith, & Barclay, 2012). Associated impairments include epilepsy (29%), speech (>60%), vision (>30%), and hearing impairments (>10%), with greater than 50% of children at 5 years having some level of intellectual impairment. CP is classified into four predominant types: spastic (85%), dyskinetic (6%), ataxic (5%), and hypotonic (3%). The majority of injury occurs in the perinatal period (94%); however, CP does occur in early childhood. Prematurity and low birth weight are known risk factors for CP; however, for many infants, the complete causal pathway remains unclear. It is often associated with factors such as birth asphyxia, congenital infections, birth defects, sentinel events such as acute and sustained fetal bradycardia, head trauma, or cerebral infarctions (Smithers-Sheedy et al., 2016).

The average age at which a child receives a diagnosis of CP is approximately 18 months. However, earlier identification is important as the optimal time for neuroplasticity, and therefore, the opportunity for targeted EI is in the young infant. Within the past few years in some neonatal units and follow-up clinics, there has been a significant shift in focus from a referral for EI with a confirmed diagnosis of CP to the referral of babies deemed to be "at risk" of CP (McIntyre, Morgan, Walker, & Novak, 2011) related to the implementation of the general movements (GMs) assessment into clinical practice within many neonatal units. The GMs assessment evaluates the quality of movement in infants to approximately 5 months post-term age. Research has shown that the GMs is a strong predictor of CP in the preterm infant and has also been shown to be useful when used with infants requiring major surgery (Crowle, Galea, Walker, Novak, & Badawi, 2018). It is important, therefore, that neonatal nurses should have knowledge of the risk factors and tools available for early identification of babies with CP or those in the neonatal units deemed to be "at high risk" of CP. Neonatal nurses have an integral role, not only in saving the lives of small and sick neonates, but preventing disability and in the early identification of these "at-risk" infants.

In 2017, the landmark international guidelines were published, providing contemporary evidence-based data on optimal early diagnosis and intervention for children with CP. These guidelines state that CP can be predicted with a high degree of accuracy in infants less than 5 months of age using the GMs assessments, the Hammersmith Infant Neurological Assessment (HINE), and neuroimaging with magnetic resonance imaging (MRI; Novak et al., 2017). They also provide data to guide early detection of infants in low- and middle-income countries (LMICs) where imaging may not be available. Neonatal nurses should be aware of these guidelines as increasing evidence supports the value of EI in improving outcomes: The earlier the CP is identified, the more optimal the outcomes are. As CP is a lifelong condition, parents require accurate information regarding the outcomes, interventions, and supports available (Ballantyne et al., 2018). Neonatal nurses must consider that the priority is not only saving lives but consistently implementing neuroprotective strategies to prevent or minimize disability. These include, but are not limited to, skilled biochemical knowledge, gentle handling and positioning, minimizing stressors and reducing pain, optimizing nutrition and growth, and supporting families in the care of their baby. Babies identified as "at risk"

can be referred for intervention to therapists while in the NICU, and families may be referred to CP-specific services when they leave the neonatal unit. Neonatal intensive care transcends from the immediate focus on survival to the long-term infant.

Rehospitalizations and Readmissions

The health issues of NICU graduates can be complex and numerous. The associated costs of the hospital and posthospital care, readmissions, and rehospitalizations are enormous as well (Arth et al., 2017; Barradas et al., 2016; Frawley, 2017; Grosse, Waitzman, Yang, Abe, & Barfield, 2017; McLaurin, Wade, Farr, & Franklin, 2017; McLaurin, Hall, Jackson, Owens, & Mahadevia, 2009; Underwood, Danielsen, & Gilbert, 2007). In 2013, in the United States, the cost of birth defects' hospitalizations only was estimated at $23 billion (Arth et al., 2017). Readmissions in the NICU patients, especially in preterm infants, can be twice as high as those in the term group, even when there is good follow-up care (McLaurin et al., 2009). In today's healthcare market and with the move toward the creation of accountable care organizations (ACOs), the concerns are growing around increased costs related to readmissions. Population-level study in the United Kingdom showed that 5% of healthy infants were readmitted within the first 30 days after birth (Harron, Gilbert, Cromwell, Oddie, & van der Meulen, 2017). The rates of readmission in preterm infants can be much higher (up to 50%) depending on the initial neonatal health problems, comorbidities, and adequacy of postdischarge and follow-up care, especially in the first 3 months after discharge (Bird et al., 2010; Girgin & Güler, 2017; Kuzniewicz, Parker, Schnake-Mahl, & Escobar, 2013; Ralser et al., 2012; Spicer et al., 2008). Readmission rates are also related to postdischarge mortality rates. In infants weighing less than 1,000 g and less than 27 weeks of gestation, De Jesus and coworkers found that post-NICU discharge mortality rate was 22.3 per 1,000 extremely low birth weight infants, with African American race, unknown medical insurance, and prolonged hospital stay as risk factors (De Jesus et al., 2012). To understand the magnitude of this fact, it is important to note that the overall infant mortality rate in the United States in 2010 was 5.87 infant deaths per 1,000 live births (Ely, 2018). Preterm infants are likely to require readmission more often than their term counterparts: Late preterm infants had almost four times the risk of readmission compared with term infants, early preterm twice the risk, and moderate preterm 2.5 times the risk (Kuzniewicz et al., 2013; McLaurin et al., 2009). Surgical patients also have a high incidence of readmissions. South and colleagues reported that 40% of NICU graduates with gastroschisis were readmitted, and 65% of readmissions occurred during the first year of life (South, Wessel, Sberna, Patel, & Morrow, 2011). Readmissions were not associated with gestational age, birth weight, or the length of hospital initial stay; one of the main reasons was abdominal distention/pain. In children with CHD, readmissions occurred in one in five infants within 1 month after discharge (Mackie, Ionescu-Ittu, Pilote, Rahme, & Marelli, 2008); data from the U.K. national cardiac audit (2005–2010) showed that up to 7% of infants with CHD were readmitted within 1 year after discharge (Crowe et al., 2015). The first weeks and months following discharge are the times of highest risk for readmissions, especially if the mother is a teenager (Ray, Escobar, & Lorch, 2010). Emergency department visits are much more costly than primary care visits, yet families often feel they need the expertise of an acute care facility. The use of the hospital versus primary care services needs further research, as does the impact of parents' readiness for the transition to home on readmissions. Providing care for parents after discharge is just as important as providing family-centered care in the NICU.

Postdischarge Family Care

The concept of the family as a unit is another important issue for providing adequate care for infants after discharge. Postdischarge care should focus not only on the mother but other family members as well. The father and siblings are often forgotten during discharge preparation and afterward despite the stress they suffer (Noergaard, Ammentorp, Garne, Fenger-Gron, & Kofoed, 2018; Prouhet, Gregory, Russell, & Yaeger, 2018). Most fathers want to participate in the care and decision making for a healthy or sick/premature newborn; they require the same support (e.g., social) as mothers (Kim, 2018). The responses of fathers are sometimes different from those of mothers, but fathers also get stressed to a large extent while the baby is in the NICU and afterward (Hynan, 2016; Noergaard et al., 2018; Prouhet et al., 2018). Siblings must also adjust to the infant, who may not seem real to them, until they are able to visit the infant in the NICU (Gaal et al., 2010; Morrison & Gullón-Rivera, 2017). Many units now encourage sibling visits to help ease the infant into the family well before the actual discharge. The change in NICU design to more single rooms and the inclusion of family areas or transition areas afford the family more opportunities to stay together as a family unit. This design provides the family with more of a homelike atmosphere while offering more privacy to them (White, 2011). This concept of care needs to continue following the discharge.

CARE FOR PARENTS AFTER HOSPITAL DISCHARGE

Parenting and caring of the vulnerable infant upon coming home can be very challenging for parents. AAP Committee on Fetus and Newborn (2008) guidelines for discharge of the high-risk infants state that the "infant may be discharged before one of the infant's physiological competencies has been met, provided the health care team and the parents agree that it is appropriate, and suitable plans have been made to provide the additional support needed to ensure safe care at home" (p. 1121). These guidelines also state that parents should be actively involved and prepared for caring for a baby at home. Preparedness of parents for discharge and postdischarge as well as professional support are vital to ensure a successful transition home (AAP & ACOG, 2017). However, it has repeatedly been shown that mothers rarely recall all the information given to them by health professionals within the hospital: Stress related to their infant's hospitalization and at the time of discharge makes advice and teaching overwhelming (Burnham, Feeley, & Sherrard, 2013; Kenner & Lott, 1990; Loo, Espinosa, Tyler, & Howard, 2003; McKim et al., 1995; Weiss et al., 2017). Smith and colleagues found that 12% of families (N = 285) feel unprepared for discharge; those families were more likely to report feeding problems, difficulties in obtaining supplies, and the inability of the pediatrician to access the discharge summary (Smith, Dukhovny, Zupancic, Gates, & Pursley, 2012; Smith, Young, Pursley, McCormick, & Zupancic, 2009). Also, nurses need to address parental views on their infant before discharge: In pediatric populations, parents' perception of their child's health at discharge was associated with the risk of a subsequent, unplanned readmission (Berry et al., 2013). The hospitalization and discharge of high-risk and preterm newborn infants always hold certain risks for the health of the infant. These times should be considered as serious challenges for parents.

NICU Experience

Giving birth to a sick or small infant interferes with the development of the role of the parent. Try to remember the first time you walked into the NICU. What were your thoughts and feelings? We

know what ours were—an overwhelming urge to flee. Time seemed to be running. People were rushing and talking loudly; alarms were buzzing, intercoms were blaring, and doors were slamming. We suddenly felt tense, on edge, and fearful of our ability to survive in such an environment. Then we walked over to an incubator and peered in at a premature infant—born at 28 weeks' gestation and weighing less than 1,000 g—who looked as though she had been through a war. Scratches and cuts were visible. Tape cut into the infant's face to hold an endotracheal tube in place. The right arm was pinned to the bed to hold an intravenous line in place, and her legs were restrained to prevent dislodgment of an umbilical arterial line that was being used for blood gas sampling. Our hearts sank. We could never be responsible for providing care to this type of infant. We tried to summon the courage to walk—if not run—out of there. We were almost immobilized—yet we recognized some of the ventilators, intravenous pumps, and monitors. Surely, with this passing acquaintance, we could learn to work in this environment and actually care for the critically ill infant. Now more than 30 years later, the units are quieter, and they look more like a home environment. Attention is paid to lighting and noise, and parents are an integral part of the environment. Yet the sense of overwhelming responsibility still resides in new health professionals.

If we feel that way, what do parents feel? Their feelings are much more intense. They have the additional fear of death of a family member, a vulnerable infant whose birth should be celebrated and yet a sense of doom clouds the birth experience. For the most part, parents lack knowledge about the medical diagnosis, equipment, treatments, and routines necessary to support neonates—their baby. In the past few decades, research has repeatedly shown that the NICU environment is extremely stressful for parents and can lead to alterations in their parental role, both inside and outside the hospital, that can last a lifetime if there is no attention/intervention (Diffin, Spence, Naranian, Badawi, & Johnston, 2016; Gerstein, Njoroge, Paul, Smyser, & Rogers, 2019; Holditch-Davis et al., 2009; Holditch-Davis, Miles, Burchinal, & Goldman, 2011; Miles, Funk, & Kasper, 1992; Raines, 2013; Seideman et al., 1997). The mothers must, in addition, make a physiological and psychological postpartum adjustment. They are also in need of care, yet most mothers when asked express the need to put aside their own time for healing to focus on their infants. For the fathers, the NICU experience is also stressful (Mackley, Locke, Spear, & Joseph, 2010; Prouhet et al., 2018; Sloan, Rowe, & Jones, 2008); the need to run between two units (the postpartum and the NICU) is an added stress even if these units are in the same institution. Constraints of work are also impressive (Hollywood & Hollywood, 2011; Ireland, Minesh, Cescutti-Butler, van Teijlingen, & Hewitt-Taylor, 2016; Noergaard et al., 2018). The parents' concern for their partners and their children often forces them between the two. For the family with other children at home, the stress becomes even greater. Who can take charge of the children? How long will it be necessary for another person to help with family responsibilities? Is someone who can or will step in to help even be available? These are very real family concerns that continue to exist after hospital discharge of the former NICU infant. New challenges also occur—questions about care to give to the infant, infant development, and the future. Along with these concerns comes the assumption of the new parental role. This role adjustment occurs for both first-time and experienced parents. It requires a change from a previous functional pattern to a new one. This change marks a developmental passage or transition.

Transition

Throughout life, events necessitate change. These life changes are often viewed as turning points. In the case of an NICU family, these turning points are the birth of a sick or preterm infant, hospitalization, and discharge from hospital and the transition to home. All these events require a new role acceptance (to accept the reality, facts about their infant's health), an adjustment or change in role, a setting of new priorities, and an examination of expectations. Taking on a new role requires energy, commitment, and, most of all, a change in the pattern of functioning—thus a transition. Transition involves change—leaving behind the familiar and trying something new. There are at least three transition processes for parents of NICU infants: transition to parenthood, transition to home, and transition to primary healthcare settings.

Transition to Parenthood. The role of parent is a good example of the transition process. For parents of an NICU infant, the transition to parenthood may have two time points—one associated with becoming parents at the time of birth and the other occurring at the time of discharge. Two important processes can be impeded in NICU parents, specifically mothers, while in the hospital: maternal role attainment (MRA) and attachment. These disturbances have consequences that may extend beyond the immediate posthospital discharge period, and both mothers and fathers can be struggling with certain problems, such as psychological distress and lower confidence in parenting (Brandon et al., 2011; Harris, Gibbs, Mangin-Heimos, & Pineda, 2018; Holditch-Davis et al., 2015; Hollywood & Hollywood, 2011; Noergaard et al., 2018; Prouhet et al., 2018; Wolke, Eryigit-Madzwamuse, & Gutbrod, 2014).

Once a pregnancy is confirmed, both mother and father begin the task of examining their individual roles. For first-time parents, this means considering what it will be like to be a mother or father to a dependent infant. For parents with other children, the new infant will bring a unique personality and another dimension to the already formed family unit. This infant, too, will require role adjustment on the part of the parents. Acquisition of the maternal role and maternal identity, as described by Rubin (1984) and Mercer (1995), focused on mothers of healthy, term infants (Mercer, 1995; Rubin, 1984). When the infant is premature or sick and does not fit the image of the desired child, women lose their normal frame of reference for the development of their own role expectations and the expectations of their infants as well. Later, MRA had been replaced with the new term, "Becoming a Mother" (BAM), as a more inclusive and comprehensive concept where maternal confidence and identity continues to grow or can be disrupted with a child's developmental challenges and life's realities (Mercer, 2004). Decreased MRA was observed with medically fragile infants due to high levels of worry in mothers and less responsiveness of infants (Miles, Holditch-Davis, Burchinal, & Brunssen, 2011); parenting quality has been shown to be influenced more by MRA than by child illness severity (Holditch-Davis et al., 2011).

The immediate process of attachment, a formation of a relationship between a parent and her or his newborn infant, occurs with wanting the pregnancy, positive maternal feelings, seeing the infant soon after birth, and immediate contact with the infant after birth (Bialoskurski, Cox, & Hayes, 1999; Vazquez & Cong, 2014). Delayed and problematic attachment occurs with a premature infant; uncertain outcomes; a handicapped child; poor maternal health; prolonged care that limits the family's ability to touch, hold, and protect their infant; a poor attitude in the partner; a lack of social support; drug dependency; and a taking-one-day-at-a-time attitude (Spinelli et al., 2015; Zabielski, 1994). Attachment, which is considered a dyadic process, becomes a triadic relationship in the NICU, in which NICU personnel—especially nurses—can alter the process. The mother of a premature infant is also a premature mother. Not only are the binding-in and claiming processes affected, but the mother herself is a "preemie" as well. Her pregnancy has ended before her own expectations were met and

needs were fulfilled. The interactive and therapeutic relationships between a nurse and a mother foster the process of BAM; moreover, instructions without nurse input are not effective (Mercer & Walker, 2006). Nurses can hinder or facilitate a mother's attachment to her infant by encouraging mother–infant touch or by forbidding it. Provision of accurate information about the infant's care, health status, and ongoing communication can facilitate the formation of attachment and bonding (Cox & Bialoskurski, 2001; Mäkelä, Axelin, Feeley, & Niela-Vilén, 2018) as well as improve interactions between parents and healthcare professionals (Epstein et al., 2017). Nurses at the NICU were named as the best source of information that helped parents to understand infants' medical conditions (Kowalski, Leef, Mackley, Spear, & Paul, 2006). Research has also shown that a decrease in maternal stress as well as a decrease in early separation during hospitalization can prevent the development of distorted attachments in mothers of preterm infants (Korja, Latva, & Lehtonen, 2012). Also, those mothers can form balanced attachments with their infants, and maternal–infant interaction may be more positive and of higher quality than in mothers of full-term infants if maternal stress is managed and their interaction is fostered prior to and following discharge (Korja et al., 2012; Treherne, Feeley, Charbonneau, & Axelin, 2017).

In addition to possible affected attachment and development of parental role, the actual assumption of the new parental role can be quite overwhelming. Even when a healthy newborn is brought into a family, stress and even crisis can occur (Emmanuel & St John, 2010; Miller & Sollie, 1980). Some researchers and clinicians view transition to parenthood as a *crisis* rather than just a developmental passage to a new functional level. Since the 1970s, research has shown that families see birth hospitalization and bringing home a premature or ill infant who has been in the NICU as a crisis (Affleck & Tennen, 1991; Caplan, Mason, & Kaplan, 1965). Even parents of low-risk premature infants suffer from distress (Jones, Rowe, & Becker, 2009). During hospitalization, parents often suffer from acute stress disorder (Helle, Barkmann, Ehrhardt, & Bindt, 2018; Jubinville, Newburn-Cook, Hegadoren, & Lacaze-Masmonteil, 2012) that can exist for a longer time after discharge as posttraumatic stress disorder (PTSD; Helle et al., 2018; Kersting et al., 2004; Shaw et al., 2009). Symptoms of PTSD include (a) reexperiencing the phenomenon (NICU traumatic experience); (b) avoiding thoughts, feelings, places, and people associated with the event; and (c) hyperarousal symptoms (such as irritability, startling easily, anger, and difficulties with sleeping; Mowery, 2011). One national survey showed that 9% of new mothers experience PTSD (Beck, Gable, Sakala, & Declercq, 2011). Even if the infant requires no special equipment postdischarge or does not suffer from the initial neonatal disorder, the family may still experience PTSD related to the initial hospitalization and long-term consequences of initial psychological trauma for family. Recent research showed that parents of high-risk newborns often had higher levels of PTSD symptoms and depression; for an entire family, parenting of high-risk neonates led to fewer years of education of family members, higher unemployment, lower incomes, distortion of marital relationships, and family strain (Cook, Ayers, & Horsch, 2018; Placencia & McCullough, 2012). Fortunately, the negative effects of neonatal hospitalization on family functioning, quality of life, and child behavior have been shown to decrease with time, and the family may adjust well, even with a neurosensory-impaired child (Hall et al., 2017; Saigal, Pinelli, Streiner, Boyle, & Stoskopf, 2010). A recent study reported an unclear role of PTSD on infant development (Cook et al., 2018). Rautava, Lehtonen, Helenius, and Sillanpaa (2003) followed 170 Finnish preterm infants and their families for 12 years. At 3 years of age, children in a high-risk group were reported as having more sleep and behavioral problems compared with those in a low-risk group; all of these differences disappeared by the time the children were 12 years old (Rautava et al., 2003). In Saigal et al.'s (2010) study that examined the impact of illness in young adults born with extremely low birth weight at age 20, mothers reported that caring for their child with neurosensory impairment had even brought their family closer together (Saigal et al., 2010). What is important is helping families to cope with initial transitions after hospital discharge. At 2 years after discharge, social isolation, financial burden, unpaid time off from work, issues related to home safety, and enrollment to the EI programs were the important issues revealed by parents of preterm infants and infants with CHD (Brown & Smith, 2018; Lakshmanan et al., 2017).

Two other major problems can occur when parenting high-risk and preterm infants after discharge. These are vulnerable child syndrome (VCS) and compensatory parenting. Parental responses to their infant are mediated by the infant's illness, the hospitalization, and "near-miss" events. The VCS is one such response that has an impact on both the infant and parents. Green and Solnit (1964) hypothesized that, when children are expected to die prematurely or were seriously injured, the result is a disturbed psychosocial development of the family, based on the parent–child relationship (Green & Solnit, 1964). Because the child is seen as "vulnerable," parents overprotect the child, make more visits to healthcare providers for relatively minor illnesses, and may discipline the child in a gentler manner, which may result in behavior problems (Kokotos & Adam, 2009; Levy, 1980; Tallandini, Morsan, Gronchi, & Macagno, 2015). It has been shown that even neonatal jaundice and inpatient phototherapy can contribute to the VCS development because the infant is labeled as sick and vulnerable by the parents (Usatin, Liljestrand, Kuzniewicz, Escobar, & Newman, 2010). What is important is the fact that VCS is a family disorder cyclically affecting both parents and children (Chambers, Mahabee-Gittens, & Leonard, 2011; Greene, Rossman, Meier, & Patra, 2017). Allen et al. (2004) found that higher maternal perception of child vulnerability was associated with worse developmental outcomes and lower adaptive functioning in preterm infants less than 32 weeks of gestation with CLD at 1-year adjusted age. The mothers who perceived their children as more vulnerable were more anxious, more depressed, and perceived a greater impact of illness on the family; longer hospitalization and maternal anxiety at discharge predicted higher perception of child vulnerability (Allen et al., 2004). Research has shown that maternal adaptation during the neonatal period and maternal self-inefficacy beliefs about feeding the infant predicted the mother's later perceptions of the infant's vulnerability at the first 4 months of corrected age (Teti, Hess, & O'Connell, 2005). Thus, maternal attachment, development of parental role, and perception of the infant health influence the entire postdischarge well-being of the family and infant.

Compensatory parenting is another disturbance when parenting an initially hospitalized child. This parenting style is compensation for feeling sorry for or guilty about having an infant in the NICU (Miles & Holditch-Davis, 1995). Parents try to provide special experiences for their infants born preterm and avoid other experiences; sometimes more stimulation to foster development with these children is provided. At the same time, they have shielded their children from other life situations to protect them from further hurt, viewing them as "special" and "normal" at the same time (Miles & Holditch-Davis, 1997).

Disturbances in parenting occurring in parents are tightly related to parental psychological well-being. Anxiety and depression have been documented in parents of high-risk and preterm infants, both in the hospital and postdischarge, and especially

in low-income families (Enlow et al., 2017). At discharge, 43% of mothers of preterm infants had moderate-to-severe anxiety, and 20% had clinically significant levels of depression (Rogers, Kidokoro, Wallendorf, & Inder, 2013). Importantly, maternal anxiety and depression at the NICU was shown to be predictive of adverse interactive behaviors, lower child cognitive development, and behavioral problems in infants weighing less than 1,500 g at later ages (McManus & Poehlmann, 2012; Zelkowitz, Na, Wang, Bardin, & Papageorgiou, 2011). Fortunately, it has also been reported that parental distress, depression, and anxiety decrease over time and sometimes have no negative impact in terms of parenting; however, correlation of depression can be different at discharge and a few months later (Hall et al., 2017; Mew, Holditch-Davis, Belyea, Miles, & Fishel, 2003; Padovani, Carvalho, Duarte, Martinez, & Linhares, 2009). In addition, on a positive note, a recent study showed that participation in EI programs was not limited by depressive symptoms in mothers (Feinberg, Donahue, Bliss, & Silverstein, 2012).

"Searching for normalcy" and grief are other aspects of parental challenges (Benfield, Leib, & Reuter, 1976; Golish & Powell, 2003; May, 1997; Tomlin, Deloian, & Wollesen, 2016; Valizadeh, Zamanzadeh, & Rahiminia, 2012; Whittingham, Boyd, Sanders, & Colditz, 2014). Mothers are searching for normalcy in their lives through caring of the low birth weight infants when they are at home; learning caregiving, maintaining vigilance for infant's progress, normalizing with caregiver burden, and help seeking are main themes (May, 1997). Contradictory feelings of joy and grief are also present in parents of preterm infants who lost the "ideal child" and are often unable to communicate that feeling of loss (Golish & Powell, 2003). Unresolved grief may lead to insecure attachment and inadequate interactions between mother and baby (Shah, Clements, & Poehlmann, 2011). What is important here is that the normal grief response can become a chronic sorrow in parents who have a child with permanent, progressive, or cyclic health problems; this chronic sorrow can even become a pathological grief (Gordon, 2009).

Transition to Home. Although the NICU discharge is the overriding goal for the healthcare professional and the family, the actual transition to home can be a time of crisis for the family. Transition to home can be even more difficult for parents than the period of the infant's hospitalization because parents are moving from a safe hospital environment to home and taking all the responsibilities for the care of their vulnerable infant (Ballantyne et al., 2017; Murch & Smith, 2016). For many parents, the NICU reinforces learned helplessness. Parents express the need to understand their role and what is expected of them in relationship to their infants' care needs; yet they feel "in the way" and unable or incapable of caring for their infants. Thus, they learn to be helpless. The picture changes, however, at the time of discharge when parents move from the safety net of the hospital to independent caregiving at home and accepting total responsibility for their infants. The parents are told, "Now it is your turn." It is no wonder that this discharge can be cognitively appraised as being a stress and that early parenting problems, possible risks in relationship development, can affect both family and the infant (Anderson, Riesch, Pridham, Lutz, & Becker, 2010; Lutz, Anderson, Riesch, Pridham, & Becker, 2009). Parents should be a part of the NICU healthcare team in order to fully understand what is wrong with their infant and to feel able to make decisions. When given the opportunity to discuss their concerns, parents are vocal about their feelings regarding their NICU care and preparation for discharge. One family stated, "The only time that the physicians really asked us our opinion or told us about the baby's condition was when they were obligated to get informed consent for an experimental treatment." Another family said, "We would ask the nurses about the baby's apnea, but they said they had to check with the physicians and they would have to talk to us." Other comments included, "I never understood why nurses just came over and turned off our baby's sounding alarms without seemingly looking at the baby."

Preparedness for discharge is vital. Information is critical to the successful transition home. Recent studies show that families are not always well prepared for discharge, and especially those with limited English proficiency (Berman et al., 2018; Obregon, Martin, Frantz Iii, Patel, & Smith, 2019; Smith et al., 2012). Even when parents report that they are prepared at discharge, parents can be naively confident in caregiving and, in fact, be unable to provide proper care at home (Hess, Teti, & Hussey-Gardner, 2004). It can be assumed that inadequacy of caregiving and skills when caring for vulnerable infants may affect the health status of an infant and lead to readmissions or overuse of healthcare services. This assumption needs further research.

Transition to home can be especially challenging for parents if the infant requires technology at home or has specific healthcare needs. All the healthcare needs of the infant often require advanced knowledge and skills from parents and primary healthcare providers. One study showed that 19% of moderately preterm infants were discharged home with ongoing medical needs and the use of durable medical equipment such as apnea monitors, oxygen, or feeding tubes (Kirkby, Greenspan, Kornhauser, & Schneiderman, 2007). All these ongoing healthcare needs require additional support and education of parents postdischarge. Feeding issues (such as tube feedings, food intolerance, breastfeeding problems, and formula selection) as well as developmental concerns bring enormous stress on parents (Lutz, 2012; Sanchez, Spittle, Slattery, & Morgan, 2016; Spiegler et al., 2013). More than two decades of research showed that the needs in informational support in parents of infants is very high, both when healthy and sick, both in the hospital and afterward (Boykova, 2016a, 2016b; Brazy, Anderson, Becker, & Becker, 2001; De Rouck & Leys, 2009, 2011; Kenner, 1990; Kenner & Lott, 1990; McKim, 1993; Radecki, Olson, Frintner, Tanner, & Stein, 2009). Parents often feel unprepared (Sneath, 2009), and especially adolescent mothers (Enke, Oliva y Hausmann, Miedaner, Roth, & Woopen, 2017; Hymas & Girard, 2018; White-Traut et al., 2017). Importantly, knowledge and skills needed by parents sometimes differ from those provided by health professionals (Drake, 1995; Toral-López et al., 2016), and fulfilling individual information needs of parents is vital. Even assuming that some infants have to be rehospitalized due to medical conditions and parent education might have little effect in such cases (Klein, 2011); transition from hospital to home remains to be dependent on the levels of parental knowledge and skills, competency and confidence in caring for an infant, and availability of professional and social supports. Yet there is limited research on transitional problems in parents of NICU patients, as well as solid theoretical frameworks and validated measurement tools. Some concepts of transition for parents of NICU infants are presented in Figure 37.4. One of the available models and instruments is described as follows.

Example of Theoretical Framework on Parental Transition From NICU to Home. One theoretical model has been developed in the 1990s for parents of NICU patients who transitioned from hospital to home—the Transition Model developed by Kenner and colleagues (Flandermeyer, Kenner, Spaite, & Hostiuck, 1992a, 1992b; Kenner, 1988, 1990; Kenner & Lott, 1990). A series of studies were conducted on parents of both term and preterm infants after hospital discharge. Five main parental transitional challenges were identified in the immediate postdischarge period: Informational Needs, Parent–Child Role Development, Stress

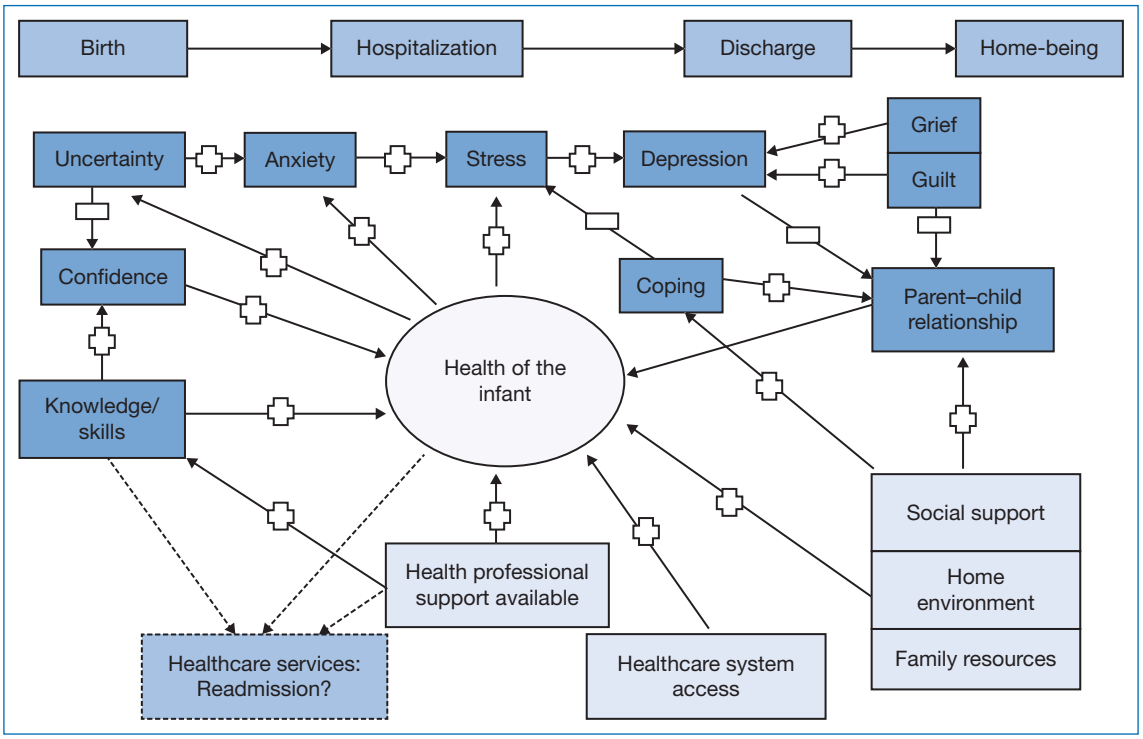

FIGURE 37.4 Concepts involved in transition derived from the literature and possible relationships among parental challenges, knowledge, infant health, professional support, and readmissions.

and Coping, Social Interaction, and Grief. Despite the changes in neonatal intensive care and health provision, these concepts are still standing for transitional concerns of parents of high-risk infants who were hospitalized after birth.

Informational Needs. The informational needs of parents include the following:

1. How to provide routine newborn care (e.g., feeding, bathing)
2. How to recognize normal newborn characteristics, both physical and behavioral (amount of "normal" crying) as well as any warning signs
3. How to keep the infant healthy after discharge (i.e., immunizations)
4. How to recognize if their infant is not well; sleeping and awake periods
5. Infant development and prognosis for future
6. Equipment used on their infant at home if any. During home follow-up, parents, particularly mothers, want more information about feeding, formula, breastfeeding, elimination patterns, weight gain, and the infant's breathing pattern.

Parent–Child Role Development. This category refers to parents and children's role expectations that are influenced by the development of relationships and interactions with an infant, which can be impaired by the infant's initial illness or special healthcare needs and interfere with the development of parental role. For anyone making a transition or entering a new level of functioning or a new stage of life, certain expectations about what is to come exist. New parents of healthy infants adjust in how they carry out the tasks of daily living once their newborn is at home. When a problem with the infant who requires more attention or special care arises, parents may have to set aside their expectations of their roles and feel inadequate in parenting and making healthcare decisions for the infant. The parents may feel that they are not "real" parents and not capable of parenting and caring for their infant and that the physician's permission is necessary to make even the smallest change in the infants' routines that had been established in the hospital.

Stress and Coping. Stress and coping are related to alterations in parental role, uncertainty and anxiety caused by health problems of the infant, and parental perceptions of their abilities to care and cope with challenges at home. The expected feelings of joy and the months of anticipation of discharge to home are replaced by sharply contrasting feelings of fear, anxiety, caregiver's tiredness, and overwhelming stress. Coping abilities that have to be present to overcome the stress of discharge depend on resources available (informational, material, and social).

Social Support and Interaction. The Social Interaction category includes parents' ability to socialize after their infant is born sick or preterm. Often, parents isolate themselves due to healthcare risks for their infant (such as RSV infection) or limit their social activities because of misunderstanding about their infant's health issues or if their infant is technology dependent; the feeling of isolation related to protection of a baby is prominent in contemporary research as well (Enlow et al., 2017; Gullino et al., 2017). On the other hand, family and friends may be frightened to approach the parents for fear of doing or saying the wrong thing, thus isolating parents of a vulnerable infant. Social interaction depends on social support from the parental informal network, and the recipient (Kim, 2018; McKim et al., 1995) determines support from healthcare professionals, which can be viewed positively or negatively as perception of the support. Recent studies on transition from hospital to home showed that support improves confidence in care as parenting a high-risk or preterm infant can be socially disruptive (Adama, Bayes, & Sundin, 2016; Ballantyne et al., 2017; Boykova, 2016a).

Grief. Grief found in parents of NICU infants is related to loss of the image of an "ideal" infant and fear of the infant's ultimate death that influences relationships between the parent and infant within the family as a whole and social interaction. Parents express the loss of their expected child once the reality of the neonatal problem shatters their hopes and fantasies. As time goes on, parents continue to grieve but in the form of anticipating that the infant

would eventually die if he or she would be sick enough to require special care or have developmental problems. The process of grief and the period of mourning begin once the infant does not meet the parents' expectations of the fantasy or ideal child. If the parents have other children, they may speak of how different this child is from their other children or how different the infant is from their expectations. Another component of grief is the loss of the expected parenting role—that is, their normal role. Some or all of the social rituals that socialize mothers into their impending role and prepare them for their new responsibilities—such as baby showers, parenting classes, and birth announcements—may often have been absent with the birth of a premature or ill infant. Friends and family who would normally be happy to help celebrate the joyous occasion of birth with the exuberant parents may feel uncomfortable and helpless around them, thus withdrawing needed psychological support.

These categories form the basis for transition to home and have not changed in almost three decades (Boykova, 2016b; Boykova & Kenner, 2012). These five categories of parental concerns represent the taxonomy for transitional care follow-up. All concepts are interrelated, and relationships between them are reciprocal, with Informational Needs being the core category. The main feature of the model is that transition is viewed as a process, not the product or outcome of changes that were brought to parents with the birth of a vulnerable child. Hospitalization of an infant is the key factor that might influence postdischarge transition to home. This assumption was confirmed in other studies through the years: Kenner (1988) and Bagwell (1990) found that parents from Level II and III units had similar concerns after hospital discharge; Boykova (2008) did not find any correlation between parental transitional concerns and birth weight or gestational age of former NICU infants (see the depiction of the model in Figure 37.5; Bagwell, 1990; Boykova, 2008; Kenner, 1988); a recent UK study also revealed information needs in parents of high-risk infants (Tregay et al., 2016).

The Transition Model has a specific multidimensional tool for the measurement of transition challenges in parents of NICU infants—the Transition Questionnaire.

Transition Questionnaire. The original Kenner Transition Questionnaire (Boykova & Kenner, 2012) consisted of four parts:

1. Thirty-seven statements in Likert-scale format that measure parental concerns and perceptions postdischarge
2. Three multiple-choice-format items considering certain informational needs in parents
3. Three open-ended questions related to parental concerns after discharge that they might have had
4. Demographic information part of the tool, consisting of 21 items about the parent and infant

Several items are negatively worded in order to decrease response bias; 17 items have to be reversed when scoring. Scores on each item of the Likert-scale format are summed for the total score, as well as for subscales. The possible range of scores is 37 to 185, with the larger score reflecting fewer problems after discharge. The dimensions of the instrument are Informational Needs (6 items), Stress and Coping (15 items), Parent–Child Role Development (9 items), Grief (4 items), and Social Interaction (3 items). The item readability level is the fifth grade; time to complete the tool is approximately 15 to 25 minutes. Examples of the items are (a) "I feel competent in caring for my child," (b) "I have trouble sleeping at night because I worry about my child," (c) "I believe no one really understands how I feel," (d) "The people I live with have been supportive of me," (e) "I cannot control my child's health." The development of the instrument has been described elsewhere;

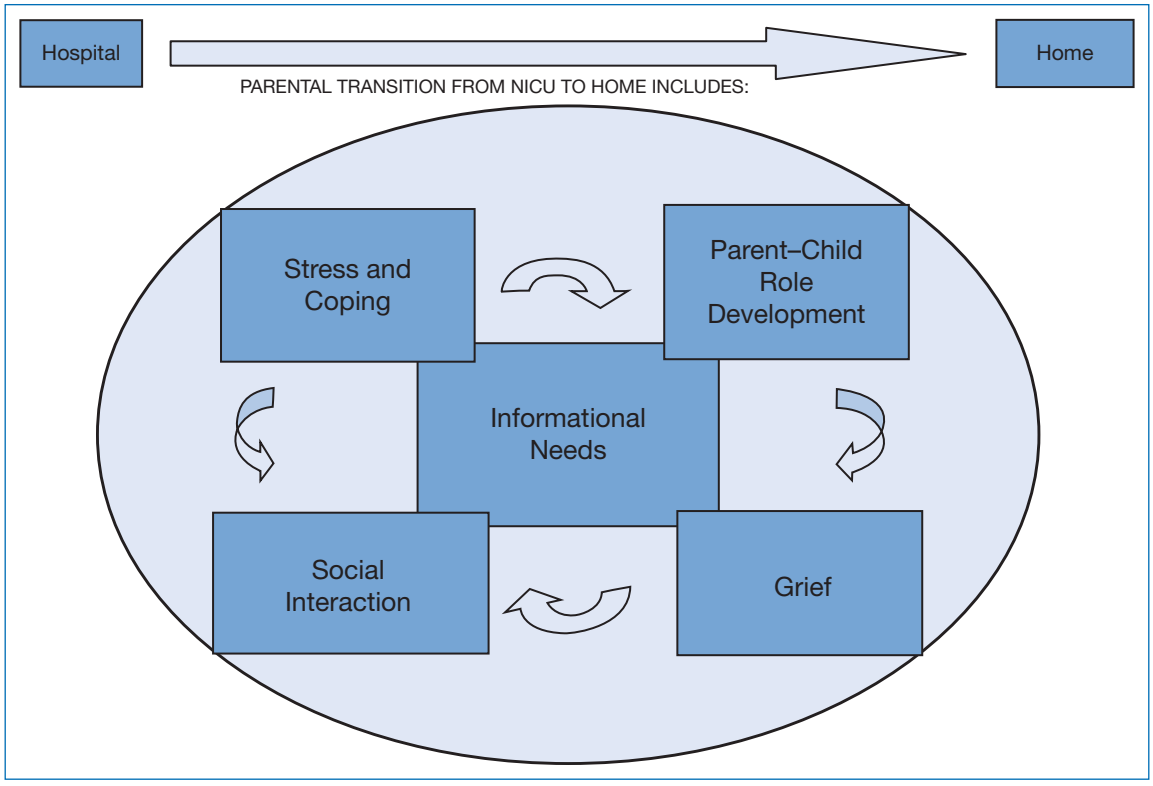

FIGURE 37.5 Hypothesized depiction of the concepts in the Transition Model.

Sources: From Kenner, C. (1988). *Parent transition from newborn intensive care unit to home* (Doctoral dissertation). Indiana University, Indianapolis, IN. Retrieved from http://openlibrary.org/works/OL2733775W/PARENT_TRANSITION_FROM_THE_NEWBORN_INTENSIVE_CARE_UNIT_(NICU)_TO_HOME; Kenner, C. (1990). Caring for the NICU parent. *Journal of Perinatal and Neonatal Nursing, 4*(3), 78–87. doi:10.1097/00005237-199012000-00010

both the Transition Model and instrument warrant further development and validation (Boykova & Kenner, 2012).

Recently, the questionnaire was revised, updated, and tested (Boykova, 2018). Based on three studies conducted in 2012 to 2015, the items were revised, and exploratory factor analysis (principal axis factoring with oblimin rotation) on the construct of transition in parents was performed. The original version of the questionnaire was reduced to 17 items in four major dimensions, as reported by parents (N = 704): *Isolation*, *Worry*, *Confidence*, and *Professional Support*. It seems that in the era of a vast amount of online resources, parental informational needs transformed into more prominent and more important, for parents, professional support after discharge. The revised instrument demonstrated adequate psychometric characteristics; however, the tool requires further testing and validation as well as five major factors revealed in the study.

Transition to Primary Health Care. The third type of transition in parents and infants in the postdischarge period is the transition to the primary healthcare settings. Continuity of care, comprehensiveness, timeliness, and appropriateness of posthospital care can influence the health of an infant and family tremendously. Often, parents have difficulties in finding primary care providers who would be experienced and knowledgeable about NICU populations' needs and risks. Research in the population of adult patients has shown that:

1. Less than half of the patients are able to list their diagnoses, medications, and their purpose or adverse effects after discharge.
2. Up to 20% of the discharge summaries lack information about hospital treatment.
3. Up to 40% of summaries do not mention discharge medications.
4. Ninety-two percent of discharge summaries lack information of patient or family counseling (Kripalani et al., 2007; Makaryus & Friedman, 2005).

The linkage between patient readmissions, avoidable complications, and appropriateness of postdischarge care has been well documented in the population of adult patients. The Transitional Care Model of Dr. Mary Naylor and colleagues from the University of Pennsylvania is an example of a practice model that has been proven to be effective and efficient in the population of elder/older patients with various medical conditions (Naylor et al., 2004; Naylor, Aiken, Kurtzman, Olds, & Hirschman, 2011; Naylor, Bowles, et al., 2011). This model provides in-hospital planning and home follow-up for chronically ill high-risk patients, with a transitional care nurse as an assigned leader and coordinator for a multidisciplinary transitional care team of medical doctors, social workers, discharge planners, pharmacists, and other members of healthcare teams (Naylor et al., 2009). More recent study on transition to home in high-risk NICU infants also showed that home visits by social workers and family resource specialists reduce readmissions and thus healthcare use and medical spending (Y. Liu et al., 2018); moreover, parent–infant interaction seems to be improved after home visits as well (Goyal, Teeters, & Ammerman, 2013).

Less is known about parents of NICU infants after discharge. A recent online survey on parents of preterm infants (N = 52; 99.9 were mothers) conducted with the help of the moderator of the blog from PreemieWorld, Deb Discenza, revealed that only 44.2% of parents participated in transitional care/follow-up programs (Boykova, 2016a). Parents often had difficulties with getting appointments and finding specialists who would manage their infant's medical problems after discharge (such as pulmonologist, pediatrician, dietitian, developmental specialist, and lactation specialist). Despite the expansion of developmental and family care principles all over the world during recent decades, in this pilot study, 77.1% of parents had been separated from their infants during the hospital stay, and 41.7% could do only a small amount of caregiving while in the hospital. At least one rehospitalization after discharge occurred in 52.4% of cases. However, parents who were participating in transitional care programs were very satisfied with healthcare. And yet, attendance can be a problem. In Canada, where healthcare coverage is universal, Ballantyne, Stevens, Guttmann, Willan, and Rosenbaum (2012) found that attendance in follow-up programs decreased during the first 12 months from 84% to 74%, and the higher withdrawal from the programs occurred after NICU discharge, followed by withdrawal after the first appointment (Ballantyne et al., 2012). The reasons provided by mothers for nonattendance were not completely clear, as they were not fully reported. From the limited data this study could collect from mothers (two thirds did not voluntarily provide reasons), the main nonattendance reasons were preference to be followed closer to home or by different healthcare provider (pediatrician). Hypothesized reasons were reluctance of having the child assessed (especially when a disability is suspected), elevated depression, socioeconomic differences, and PTSD (Ballantyne et al., 2012). In Australia, parents of prematurely born infants preferred to use services that were instrumental in accessing needed services, provided there was consistent information, and supported parental self-efficacy in caring for their child (Pritchard, Colditz, & Beller, 2008). In this study, parents also highly evaluated NICU follow-up programs and were less reluctant to follow recommendations; the use of helplines was not helpful and led to confusion and an increase in anxiety in the early postdischarge period. At the discharge point, helping with pediatrician selection was found to be assistive for parents in preparation for taking the baby home (Smith et al., 2009); NICU follow-up clinics also facilitate participation in EI services (Greene & Patra, 2016). Families who felt unprepared to go home at the discharge point were more likely to report that their pediatrician could not access the infant's discharge summary and that they were not able to obtain needed feeding supplies for their infant (Smith et al., 2012). Unpreparedness for discharge, in addition to inadequate continuity of care and limited knowledge of primary healthcare providers, can be related to the overuse of services or avoidable readmissions. Three months postdischarge was reported as a period when parents use healthcare services most (Spicer et al., 2008). Wade et al. (2008) found that preterm infants during the first year after NICU discharge had frequent pediatric visits and prescription medications (mean 20 visits and 5.5 medications); surprisingly and unfortunately, half of the highest using infants were relatively healthy (who did not have CLD, necrotizing enterocolitis, or severe intraventricular hemorrhages; Wade et al., 2008). These findings dictate better continuity of care in the postdischarge period. Better care coordination of postdischarge services is needed in order to provide support to the family unit, ease the transition to the home, and promote positive growth and development of the infant.

Strategies to Help Families Postdischarge

Many interventions can alleviate a crisis for a family of an NICU or premature infant in a postdischarge period. Some approaches and strategies are described in the following.

Discharge Teaching and Information Giving. The NICU nurse—in the role of primary nurse, clinical nurse specialist, or neonatal nurse practitioner—can advocate for positive parental discharge. Recognizing parents' need for information about their infants and the required at-home care facilitates development of a collaborative, interdisciplinary plan of care, including discharge and follow-up. This type of collaborative plan should include the

parents' demonstrating competence and comfort with routine newborn care. The nurse should ensure that the parents are completely comfortable with bathing, feeding, and diapering their infant and with administering any special care procedures, such as medication or oxygen therapy. Information given to parents about feeding patterns of preterm infants should include differences and similarities between term and preterm infants. Preterm infants often have shorter periods of sustained sucking, whether receiving feedings from the breast or bottle. Signs of adequate intake are similar for both groups: exhibiting feeding cues on a regular basis, seven to 10 feeds per 24 hours, and five to six wet diapers and two to three stools per 24 hours. Pre- and postdischarge interventions have been shown to be effective for the duration of breastfeeding, promoting exclusive breastfeeding and improving maternal satisfaction as well as decreasing readmissions (Ahmed & Sands, 2010; Braet, Weltens, & Sermeus, 2016); if available, a board-certified lactation consultant (BCLC) should assist the mother, as continued support of the breastfeeding mother is essential to decreasing the risk of early weaning. The parents also need to be taught how the NICU infant's temperament may differ from that of a healthy newborn. Parents need to be informed and reminded that even though their infant is 6 months old by chronological age, she or he may be only 3 months old by conceptional age. Thus, the infant may act more like a 3-month-old than like a 6-month-old.

Comprehensive discharge teaching has also been advocated in NICUs for a long time. Quality of discharge teaching provided by nurses is vital. Good discharge teaching includes all this as well as developmental information and has positive outcomes on parental levels of anxiety and depression, as well as hospital costs. Melnyk and coworkers have developed a specific educational-behavioral program for parents of NICU infants, the Creating Opportunities for Parent Empowerment (COPE), which works in the hospital and postdischarge. The program consists of audio-taped information and workbooks for parents; parents are taught about behavior and development and caring for their infant. Teaching parents occurs in four phases, the first of which starts at an NICU. This program has been proven to be effective and efficient; the cost savings for healthcare systems are estimated at more than $2 billion per year if the program would be routinely implemented in NICUs across the country (Melnyk et al., 2010; Melnyk, Crean, Feinstein, & Fairbanks, 2008; Melnyk & Feinstein, 2009). Parenting Preemies is another program that helps parents to ease the transition to home, with educational materials, follow-up telephone calls, and home visits lasting 10 weeks (Willis, 2008). Such programs bring needed support and reassurance to parents, as well as contributing to continuity of care. Importantly, advice on financial issues, insurance coverage, and available programs is often needed, too (Discenza, 2009). Use of technology, for example, a smartphone application, NICU-2-HOME, may also provide support to parents of vulnerable premature infants as they leave the NICU (Garfield et al., 2016).

Communication and Continuity of Care. Parents often report that they feel supported and reassured if a professional in addition to family or friends advise them (Lindberg, Axelsson, & Öhrling, 2009). However, many parents also express the frustration of trying to build rapport with medical and nursing staff in primary healthcare settings. Follow-up nurses, nurse practitioners, should recognize that it could be difficult to build trust and rapport with parents who have suffered and been traumatized by their infant's hospitalization and health problems. Communication is the key element to successful relationships. Nurses are expert communicators, as the art of nursing has revolved around the ability to convey care and personal attention to the patient. Unfortunately, because of today's healthcare crisis, nursing shortages have resulted in staff mixes and use of unskilled personnel, coupled with economic constraints resulting in shortened hospital stays; nurses are also falling into the trap of assembly-line healthcare delivery. However, nurses have the advantage of being able to identify and assess a family's needs and to convey these needs to other healthcare team members. Being an advocate for the family is an essential part of preparing a family for discharge. Follow-up, in essence, is allowing an open line of communication among healthcare professionals, the healthcare delivery system, and the family. It allows a partnership to develop between the healthcare team and the family. It gives the family back some control. Follow-up moves the family away from the learned helplessness acquired in the hospital to a more participative role. Families who want to vent feelings and concerns often seek out nurses—as long as the family feels that the nurses care enough to be concerned. Parents need to be able to openly express their concerns without fear of being judged as "bad" parents. Nonverbal cues can get in the way of communication. The nurse's expertise, knowledge, and use of medical terminology without explanations all convey the nurse's need to be in control. Someone has to be in control, but relinquishing some control to the family does not lessen one's credibility as a professional. It conveys to the family that they have a role in their infant's care and that they are important, too. Importantly, nurses also need to convey information and coordinate the data between physicians, social workers, counselors, and other members of the healthcare team who work with the family. Application of the nursing process may sound trite, but it is important in terms of not only collecting data but also using the data to identify problems, make nursing diagnoses, and develop a plan of care before and after discharge. Communication among the healthcare team members, including the parents, has a positive impact on the parents before and after discharge (Discenza, 2012). Collaboration among pediatric medical follow-up, parent support or psychosocial assessments at home, and obstetrical follow-up for the mother is essential. Each healthcare professional has something to contribute to the family's overall well-being. It is essential not to compete but to work with other professionals for the good of the family. It also means that each profession must share information that it receives from the family.

Social and Material Support. After discharge, social support from family members, relatives, and friends (informal social networks) is vital. Social support is an important aspect of coping and managing stress; if support is not provided, family functioning and health may suffer. Once the social support needs of the NICU family have been identified, a plan of action must be implemented. Helpful resources might be parent support groups, parent hotlines, referral to financial resources, or home care agencies. Balancing infant care with other demands is difficult, at best, and maternal fatigue is often a major issue that is associated with depression when the infant comes home (Wilson, Lee, & Bei, 2019). Acknowledgments of the mother's own physical discomfort convey a caring and supportive attitude. The caring attitude by healthcare professionals, the friendly hug, and the taking time to talk with the parents, even if it was about something other than their infant's problems, can have positive effects on parental well-being and ease their stress. Moreover, it has been shown in mothers of healthy infants that provision of psychosocial support in the postpartum period decreased the risks of readmissions (Barilla, Marshak, Anderson, & Hopp, 2010). The availability of a phone number and the potential for a home visit are always viewed as positive by parents. For many parents, the home visit provides a way to vent feelings that otherwise might be suppressed around family and friends; home visits also provide needed reassurance for parents in caring. Unfortunately, with the current healthcare insurance

coverage in the United States, few home visits are actually made, but are still available in some places and countries. In many cases, parents appreciate even a telephone call from NICU personnel.

Screening. Another important aspect of postdischarge care could be screening for depression, PTSD, and parenting disturbances. Screening for postpartum depression (PPD) in NICU parents has been long recommended since depression is a known risk following a high-risk birth (AAP & ACOG, 2017; Barkmann, Helle, & Bindt, 2018; Bergström, Wallin, Thomson, & Flacking, 2012; Gangi et al., 2013). Gray et al. found that parenting stress was heavily influenced by maternal depression (Gray, Edwards, O'Callaghan, & Cuskelly, 2012). As described in this chapter, continued stress, feelings of failure, and grieving for the loss of the fantasy child all have the potential to lead to maternal and paternal depression. Parental anxiety and the depressive symptoms should be assessed in the postdischarge period and be part of routine follow-up care (Enlow et al., 2017); PPD was associated with nonadherence infant feeding guidelines: mothers with PPD breastfed at low-intensity and added solid foods earlier (Gaffney, Kitsantas, Brito, & Swamidoss, 2014). Psychological counseling and other needed treatments should be available for parents: A recent study showed that even after positive screening for PPD, mothers rarely used mental health services (Kallem, Matone, Boyd, & Guevara, 2018). In addition, VCS needs to be considered by those providing posthospital care. Nurses are an integral part in integrating and translating the new National Perinatal Association (NPA) recommendations for psychosocial support of NICU parents into clinical practice (Purdy et al., 2017).

Home Care. With the shift from acute care hospitals to providing home care for infants, even technology-dependent infants, the postdischarge transitions can be even more challenging for parents than before. Some families are expected to set up a "mini" intensive care unit in the home, even providing lung ventilation or intravenous medications. There are several types of home care.

Types of Home Care. Home care, for most practical purposes, is classified as short-term, long-term, or hospice care. Other programs involve respite care, which is relief care for parents; day care, which is at a specialized place that provides care for high-risk infants during daylight hours; and foster care, which refers to a family or individual who takes in a child to live in their house that is not their own when the birth family cannot provide care.

Short-Term Care. Short-term care is considered by many healthcare services to be less than 6 months in duration. Short-term care of an infant at home may include phototherapy for hyperbilirubinemia, administration of supplemental oxygen to treat respiratory distress, home monitoring for apnea of the premature infant, medication administration for various neonatal conditions, and alternative feeding methods such as gavage for nutritional support. The primary caregivers in the home usually attend to these treatment modalities. Parents and families are carefully instructed about the use of any equipment placed in the home to administer healthcare. Extensive teaching before hospital discharge must convey the precise reasons for the therapy, the necessity for close observation of the infant by the caregivers, and the importance of communication and supervision by the primary care physician. In situations of short-term home care, the condition is usually self-limiting, and the home therapy can be discontinued at a predetermined endpoint. Moreover, outpatient management of discharge-delaying ABD events in a late preterm and term population was a cost-effective alternative to prolonged inpatient observation (Montenegro et al., 2017).

Long-Term Care. The point at which care becomes long term is determined by the nature of the healthcare needs of the individual. The providers of extended care and the insurers paying for the care also arbitrarily set the period for long-term care. In general, long-term care indicates that the duration of the condition and the need for care will exceed 6 months. Long-term home care addresses situations for children with disease processes such as bronchopulmonary dysplasia (BPD), short bowel or short gut syndrome, CHD, physical and cosmetic defects, neurological and metabolic disorders, and numerous other prolonged pathological conditions. On discharge, these children may require home care services performed by professional home care agencies or programs. Families gradually become integrated into the healthcare routine. The family's responsibility changes as the infant's condition changes. The primary care physician must be closely involved and should be able to rely comfortably on the caregiver's judgment for making assessments and alterations in the home care plan. Long-term home care requires open communication among the family, community physicians, tertiary resources, community healthcare providers, home medical equipment providers, and financial providers. Many hospital records are now incorporating discharge notes, especially nursing case management notes or orders for the actual discharge and home care follow-up plan. These notes are a good vehicle for communication among the community healthcare providers and the discharging hospital.

Hospice Care. Congenital anomalies are the leading cause of infant mortality in the United States and are also a major contributor to childhood morbidity, long-term disability, and loss of years of potential life. The proportion of infant deaths attributed to birth defects has remained significantly high. The HIV epidemic is improving, but it still takes its toll on the neonatal population. Those infants require specialized home care and, in some instances, palliative care. In addition, with technological advances, the ability to prolong lives has increased. Infants who are born dying do go home, where they need end-of-life (EoL) or palliative care, the care concepts that still require improvement in the neonatal field (E. R. Currie et al., 2016). When it becomes clear that an infant will no longer benefit from acute intervention, plans for healthcare should focus on physical and emotional comfort. The transition from acute care to palliative care involves the concept of hospice. Hospice care is a philosophy of caring when cure is no longer a reasonable expectation. This care is not strictly a kind of terminal care, but rather an effort to maximize current quality of life without giving up all interest in a cure. Hospice provides comfort measures and emphasizes alleviation of symptoms. Whether the infant is terminally or chronically ill, the ultimate goal is to provide an environment that comforts the child and supports the family.

Criteria for Home Care. Some hospitals throughout the country are developing specialized outreach and home care services as an extension of their inpatient services. Regardless of how services are to be provided, the decision to facilitate early discharge from hospital care to home care must be based on standards that are safe and that provide effective ongoing therapy. The infant, the family, the home equipment, and the follow-up healthcare system must meet criteria for discharge to home care.

Infant Criteria. The infant's home healthcare needs must be assessed as to technical feasibility and medical requirements. Nutritional support must be evaluated. How does the infant feed and how frequently? How often does the infant require gavage feedings, and which feeding techniques are required? Pharmacological support assessment must be evaluated. What medication does the infant need and how often? What are the desired and adverse effects of these drugs? Does the infant require supplemental oxygen, respiratory therapy treatments, or chest physical therapy? The assessment of the level of care required

must be matched to the ability and skills of the home care providers. It must be determined before discharge so that care in the home will be safe and meet the needs of the infant and family.

The specific criteria for discharge of special groups of children—such as those with BPD, short bowel or short gut syndrome, neurological disease, cardiac disease, and other pathological conditions—are addressed in the preceding chapters.

Family Criteria. The assessment of the family's commitment to home care is perhaps the most critical factor determining the success or failure of home healthcare. After extensive discharge teaching, skills development, and repeated occasions of caregiving, the family must want the child at home and under their care. They must be willing and able to devote the time and energy required to meet the physical and emotional needs of the child. These factors are essential for the well-being of the family unit. To prepare families for the discharge of their sick or high-risk infant, NICU personnel must begin teaching them as soon as the neonate is admitted to the unit. Once the family is confident and capable of meeting the needs of the infant, a home assessment should be completed. Basic facilities such as heat, water, telephone, electricity, and transportation must be available. Appropriate support systems must be set up in the home, including the technology necessary for the delivery of care. The operation of phototherapy lights or blankets, oxygen delivery systems, portable suction equipment, respiratory and cardiac monitoring systems, ventilators, and numerous other devices must be thoroughly understood by the caregivers. Clear instructions need to be given to the family members by the providers of the home care technology. Ideally, the parents should bring the equipment to the hospital, or the equipment company can help transport it to the hospital before discharge. The rationale is that the parents can be taught on their own equipment. If a problem arises, it can usually be identified before the infant's discharge. The parents should spend at least 24 hours providing total care before discharge. This time under a health professional's supervision helps the family gain confidence in their caregiving abilities. They can also be reassured that they have the proper equipment.

Home Equipment Criteria. The most common equipment needs for neonates are cardiopulmonary monitoring, oxygen, suction, and feeding implements. The family's first decision is how to select a home care equipment company. Hospital discharge planners or the nurse responsible for the discharge can make recommendations. Once the supplier has been selected and the necessary equipment identified, parent education can begin, including neonatal cardiopulmonary resuscitation (CPR). The parents should be given written instructions to take home and a checklist for the CPR procedure that can be clearly posted. If parents cannot read, visual charts outlining the steps should be made available.

A cardiopulmonary monitor is the most common equipment needed in the home. Infants who should be placed on this type of monitoring are those whose sibling died of sudden infant death syndrome (SIDS) or who are at risk for SIDS, such as premature infants. These infants are usually monitored for several months. An infant on home oxygen or one who has neurological impairment is at risk for apneic or bradycardic episodes or desaturation, thus requiring pulse oximetry. Most of the cardiopulmonary monitors have built-in memory or pneumographic capabilities that allow trends and strips to be viewed by home care nurses. Often, parents struggle with alarm limits and sounds, so appropriate teaching should be done before discharge. Online educational modules might be effective and improve parental knowledge on SIDS and promote change in parental behavior (Dowling, Barsman, Forsythe, & Damato, 2018). Parents need to understand alarm delays or oversensitivity, when to change probes, and how to respond.

If parents have an infant who requires home respiratory support, the family will need a ventilator, with oxygen and air tanks. An air compressor and oxygen concentrator may also be needed. Portable or stationary oxygen devices vary in size and the amount of time that they will last. Humidification and suctioning equipment is needed for patients with ventilation support or tracheostomies. Parents should be taught how to perform suctioning, how often, and how to adjust suction when an illness occurs that may put the infant at risk for cross-contamination. Suctioning should be performed according to individual needs of a patient and to the physician or nurse practitioner's orders. Signs that indicate the need for suctioning are the same as those used by health professionals in the NICU: restlessness, decreased color, coughing, increased respiratory effort, or sounds of congestion. Humidification of the airway is necessary for infants with artificial airways, regardless of whether or not they are on oxygen. If the airway is not humidified, mucous membranes may dry and crack, creating areas that may become infected.

These examples of home care and monitoring are the most common. Specific instructions are needed regarding which equipment is necessary and how to use it in each situation; the equipment should be obtained from the home healthcare agency that is to provide care, the hospital equipment vendors, and the home healthcare equipment vendors. Information on home use of ventilators can be obtained from the Home Mechanical Ventilation Resource Center of the American College of Chest Physicians (www.chestnet.org). If parents are primary caregivers, they should keep a log of the timing of the suctioning and the type of secretions obtained. Time of medication administration and feeds also should be recorded. An emergency backup unit must be available—whether it is housed in the home or at immediate dispatch from the equipment company does not matter, as long as it is available for times when equipment failures occur with the portable device. Battery backup is also necessary. Ideally, the nurse should make a home visit before the discharge to assess the home environment for safety hazards. For example, is the house/apartment too hot or cold? Either condition can lead to apneic spells. Are there exposed wires in the house? Peeling paint? Open flames used for cooking when oxygen is going to be used in the house? Are there any strong or chemical odors that may be harmful to a child with respiratory compromise? Is there an emergency phone? Have utility companies been notified? Is there a backup plan in case of a power outage? Is there a plan for continued health promotion, such as immunizations? All aspects of the home and the community setting should be considered when discharging the infant and family.

SUMMARY

Postdischarge care is vital for an infant and family, and no less so than intensive care provided in the hospital. Former NICU infants may suffer from numerous health problems and may have numerous healthcare needs. Parents are in need as well. The crisis of hospitalization and discharge has no time limit because it is so individual. Three major transitions can be identified in parents of former NICU and preterm infants: transition to parenthood, transition to home, and transition to primary healthcare settings; all transitions can bring challenges to the infant and family. Parental role alteration, anxiety, depression, and an increased need for professional and social supports are tremendous. Medical follow-up of NICU infants as well as helping parents to deal with postdischarge challenges are vital in order to promote infant health, development, and family well-being. The outcome of transition (i.e., readmissions, health status of the infant, parenting-style disturbances)

will depend on whether resources are available to support the individuals undergoing postdischarge challenges and may influence the whole life span of the infant and family. Application of the interventions as close to the time of the discharge as possible is vital. The crisis of neonatal hospitalization, difficulties in caregiving, and parenting of an initially sick or small infant can be alleviated by appropriate interventions and strategies. These are appropriate discharge teaching, parental participation in transitional care programs, adequacy and timeliness of follow-up, access and attendance to transitional programs and follow-up, provision of timely and appropriate resources for family and infant, continuity and coordination of care, case management, and access to home care, to name a few. Close collaboration and open communication between healthcare providers and family is required, as well as informational and technical assistance. The absence of these can lead to a less than optimal environment for the infant and child to grow.

CASE STUDY

This case study applies the Kenner Transition Model to the care of a technology-dependent infant.

In recent years, the number of technology-dependent infants discharged home has increased, because of the many early discharge programs available and the survival of extremely low birth weight infants with chronic conditions. Although a fair amount has been written about setting up early discharge programs and the positive financial rewards associated with early discharge, little research is available to look at the effects of having a technology-dependent infant at home.

Spangler-Torok (2001) studied mothers receiving and caring for their technology-dependent infants in the home and applied the concepts of transition to this unique population. The experiential descriptions were from eight mothers, aged 17 to 42, who were the primary caretakers of their technology-dependent infants. All of the mothers were interviewed within the first 4 weeks of receiving their infant into the home. Although this was a phenomenological study, it provides support for the concepts of the Kenner Transition Model.

■ **Information Needs.** Mothers in this study understood the need to learn about care and equipment so that the infant could be discharged. Mothers described moving from learning care to making judgments regarding the infant's health. Gathering information is a way of seeking control of the situation. The mothers in this study sought information to make an overwhelming experience more manageable. The mothers described their initial fear of caring for the infant at home and their ability to move beyond the fear and do what needed to be done. As more information was gathered, mothers described using their judgment in making infant health decisions. When receiving and caring for a technology-dependent infant in the home, more information seems to give mothers more control, confidence, and peace of mind.

■ **Grief.** The mothers in this study feared the infant becoming ill and requiring rehospitalization. Several of the mothers voiced concern that the infant might die. Mothers grieved over the loss of the "ideal" pregnancy and infant. Mothers would report that they were managing the home care experience, "but this is not what I planned for." Mothers grieved about the life their infants would have and vowed to give them "as normal a life as possible." Mothers worried about what others would think: "Will they think it was something I did while I was pregnant that caused this to happen to the baby?" Mothers felt the need to "warn" others that the baby was different before they approached the infant.

■ **Parent–Child Role Development.** Once they were at home, mothers in this study believed that they were getting to know their infants and that their infants were getting to know them as their mothers. Mothers reported learning things about their infants that they didn't know until they were home, such as when their fussy times were. Mothers believed that as they learned more about infant preferences and health-related behaviors, they were able to make appropriate adjustments to infant care. Regardless of whether they had other children, the mothers saw a need to adjust the parenting role and expectation to accommodate the premature infant. They realized that this infant was different and required special care—in some instances, more vigilant care. They discussed how the increased needs of this infant took time away from other children and spouses, but acknowledged that being home was easier than extended hospital visits. Most of the mothers in this study quit their jobs or school to care for the infant, which they would not have planned to do if the infant had been healthy. The mothers discussed lifestyle changes since the infant came home from the hospital, such as decreased number of outings, staying indoors more, and limiting visitors to the home.

■ **Stress and Coping.** Mothers in this study acknowledged that receiving and caring for a technology-dependent infant in the home is a lot of work. One mother stated it is "a ton of work . . . 10 times more work than a normal infant." Mothers report that more time is needed with infant care as well as with supplemental tasks, such as dealing with insurance companies, managing supplies, and checking equipment. A lot of time is required to prepare the infant for outings, and time is needed for the infant to readjust to home after outings. Mothers reported problems with infant digestion and temperament when away from home. "She may require 2 or 3 days to recover from an outing to the doctor's office." All of the mothers described the extra work and time the infant required, but most felt it was worth it to have the infant home with them. This initial anxiety decreases as the infant's respiratory status improves and the infant becomes less dependent on oxygen therapy.

Two mothers described being overwhelmed with infant care in the home and felt they faced too many demands. One mother felt torn between caring for the infant and spending time with her other children. She was "only one person" and could "only be in one place at a time." She appreciated the break the home nurses provided but felt guilty that her infant received care from others. Another mother described frustration in dealing with the equipment. She had a "hard time looking" at the feeding tube but was less bothered by the tracheotomy. She got angry when her husband gravitated toward Holly, the "normal" twin, and left all the work for Grace to her. This mother was afraid that her infant would pick up on her frustration with the equipment and feel that she didn't love her.

■ **Social Interaction.** Several mothers in this study attributed their ability to care for this infant at home to the support of family and friends. Mothers stated they could focus on infant care because others were handling household chores and running errands for them. One mother described how strangers who heard of their situation were delivering food to them. The same mother felt that their experience was probably easier than others because "so many people have pitched in to do things." In describing her experience, one mother stated, "We just needed a lot of family." Having people come and help seemed to make the experience more manageable for some of the mothers. One mother described being supported by the home care nurses. "It's wonderful to have the nursing staff here, because when you want to break down and cry, they're there to tell you, rub your hand, or your shoulder and say, 'you're doing a good job, don't think that you're not; you are.'" She was thankful for them and used the nurses for other things so that she could spend time with the infant.

Although some mothers spoke of the assistance they received, others described the lack of support from family and friends. A mother spoke of being "annoyed" with her husband. She discussed how supportive they were of each other during their infant's hospitalization and that she had assumed that would continue once they were home. She was disappointed by her husband's lack of support and assistance with infant care and home management. "Hey, we have special circumstances here, this isn't just your average baby and you need to help me," she said. Another mother described a lack of support from her husband, children, and friends. She said her husband helped with the cooking, but it took her three times as long to clean up. Although her 12-year-old daughter was old enough to help, she didn't. She also wondered why friends had not come to see her. She believed they were afraid to see the baby and, therefore, did not visit. She sometimes felt alone in her responsibility for the baby.

The experiences of the mothers caring for infants who require technology support lend credence to the Kenner Transition Model. The mothers reported a need for information, grieved for the loss of the healthy child, and found they needed to adjust their parenting roles. They felt stressed and overwhelmed. These are all concepts in the Kenner Model. Other studies report similar findings.

EVIDENCE-BASED PRACTICE BOX

For more than 30 years, issues around the transition home, discharge coordination, and follow-up care have been researched. The reality is that for parents of a premature or sick newborn, life changes with an NICU stay. The discharge, while anticipated, is not easy. The transition to home even with follow-up appointments, programs in place, and written discharge instructions is not easy for most families. There is fear that the baby will become sick again; fear that the baby might die; fear that the health professionals in primary care or the community will not know what to do the way NICU professionals do. Research studies published in 2012 to 2018 continue to support the need for more research in the area of transition from hospital to home and the need for a clearer understanding of the actual follow-up that is being done, including adherence to suggested follow-up visits and programs (Ballantyne et al., 2012; Boykova, 2018; Hutchinson, Spillett, & Cronin, 2012; Lopez, Anderson, & Feutchinger, 2012; Murdoch & Franck, 2011; Smith et al., 2012). Murdoch and Franck (2011) identified six themes from mothers transitioning with their infants to home following an NICU stay: apprehension, confidence, responsibility, awareness, normalcy, and perspective. One or more of these themes have been reported in transition research studies for more than three decades. In light of healthcare reform and the emphasis on health promotion, the time is right to use this evidence to create better follow-up programs.

References

Ballantyne, M., Stevens, B., Guttmann, A., Willan, A. R., & Rosenbaum, P. (2012). Transition to neonatal follow-up programs: Is attendance a problem? *Journal of Perinatal and Neonatal Nursing, 26*(1), 90–98. doi:10.1097/JPN.0b013e31823f900b

Boykova, M. (2018). Transition from hospital to home in parents of preterm infants: Revision, modification, and psychometric testing of the questionnaire. *Journal of nursing measurement, 26*(2), 296–310. doi:10.1891/1061-3749.26.2.296

Hutchinson, S. W., Spillett, M. A., & Cronin, M. (2012). Parent's experiences during their infant's transition from neonatal intensive care unit to home: A qualitative study. *Qualitative Report, 17*(12), 1–20. Retrieved from https://nsuworks.nova.edu/tqr/vol17/iss12/1/

Lopez, G. L., Anderson, K. H., & Feutchinger, J. (2012). Transition of premature infants from hospital to home life. *Neonatal Network, 31*(4), 207–214. doi:10.1891/0730-0832.31.4.207

Murdoch, M. R., & Franck, L. S. (2011). Gaining confidence and perspective: A phenomenological study of mothers' lived experiences caring for infants at home after neonatal unit discharge. *Journal of Advanced Nursing, 68*(9), 2008–2020. doi:10.1111/j.1365-2648.2011.05891.x

Smith, V. C., Dukhovny, D., Zupancic, J. A., Gates, H. B., & Pursley, D. M. (2012). Neonatal intensive care unit discharge preparedness: Primary care implications. *Clinical Pediatrics, 25*, 1–8. doi:10.1177/0009922811433036

PARENT VOICES

Deb Discenza

I always tell my families that they should rely on their parent instinct. If something does not seem right with their child, they should absolutely check out the problem with the pediatrician, or with a specialist. Early identification can mean a dramatic change in their child's outcomes and identifiable supports when it comes to developmental delays and diagnosed disabilities. Yet as a parent of a 30-week premature baby girl now 15 years old, I can honestly say that the parent instinct is truly the common denominator among all of the specialties outside the NICU. The parent is the expert of his or her child starting from conception. They notice tiny but crucial nuances where others would assume no general concern mainly because of their continued presence in that child's life throughout every day. And they carry the knowledge with them from doctor to doctor even when the communication between specialists is used.

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I know this all too well having watched my own daughter's progression from NICU to home and into the school years being challenging at best. Even despite my best efforts to vocalize thoughts while partnering with the pediatrician and with the specialists at hand, no one saw what I saw very early on—concerns about cerebral palsy. At various points throughout my daughter's childhood and early adolescence, I sought out help for her increasingly complicated walk, her difficulty with running. This is a child who went through early intervention, through therapies for other conditions along the way (autism, attention deficit-hyperactivity disorder [ADHD], motor coordination). It was the orthopedic surgeon who fitted my daughter for orthotics (for the "squishy ankles" I noticed as my daughter trained on an elliptical machine) that finally listened and contemplated my concerns. Two years later, at the same practice but my assuming they weren't going to diagnose her, they did. My daughter was 13.5 years old and, while mild, had spasticity and was really struggling. I felt let down by the medical and therapeutic systems in place.

If I as a mother with strong advocacy skills could not get my daughter's diagnosis in place until 13.5 years old, imagine how many families are out there with less capability and no diagnosis. Outcomes data are dependent on many factors, and it should include parent and, at one point, patient's own reporting to help drive better information, better advocacy, and proper diagnoses.

ONLINE RESOURCES

American Academy of Audiology. (2011). *Childhood hearing screening guidelines*. Retrieved from https://www.cdc.gov/ncbddd/hearingloss/documents/aaa_childhood-hearing-guidelines_2011.pdf

American Academy of Pediatrics. (2019). *Immunization schedules*. Retrieved from https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/immunizations/Pages/Immunization-Schedule.aspx

Bright Futures. Retrieved from https://brightfutures.aap.org/Pages/default.aspx

Center for Parent Information & Resource. (2017). Overview of early intervention. Retrieved from https://www.parentcenterhub.org/ei-overview

European Foundation for the Care of Newborn Infants. Retrieved from http://www.efcni.org

Families Bridge to Caring Hands. Retrieved from https://familiesbridge.com

Franck, L. (2013). *Comforting your baby in intensive care* (2nd ed.). Retrieved from https://familynursing.ucsf.edu/sites/familynursing.ucsf.edu/files/wysiwyg/Comfy%20PDF%20ENGLISH%20Dec%2017.pdf

Golisano Children's Hospital, University of Rochester Medical Center. *Program for technology-dependent children*. Retrieved from http://www.urmc.rochester.edu/childrens-hospital/pulmonology/technology-dependent.aspx

Griffin, T., & Abraham, M. (2006). Transition to home from the newborn intensive care unit: Applying the principles of family-centered care to the discharge process. *Journal of Perinatal and Neonatal Nursing, 20*(3), 243–249. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/16915057

Institute for Patient- and Family-Centered Care. Retrieved from http://www.ipfcc.org

March of Dimes. *NICU family support program*. Retrieved from http://www.marchofdimes.com/baby/inthenicu_program.html

National Dissemination Center for Children with Disabilities Center for Parent Information & Resources. Retrieved from https://www.parentcenterhub.org/nichcy-gone

National Resource Center for Patient/Family-Centered Medical Home. Retrieved from https://medicalhomeinfo.aap.org/Pages/default.aspx

Neonatal Follow-Up Programs, The Children's Hospital of Philadelphia. Retrieved from https://www.chop.edu/centers-programs/neonatal-follow-program

NICUniversity. Retrieved from http://www.nicuniversity.org

Preemie Parent Alliance. Retrieved from https://preemieparentalliance.org

Preemieworld. Retrieved from https://preemieworld.com

Saigal, S. (2015). *Preemie Voices: Young men and women born very prematurely describe their lives, challenges and achievements*. Victoria, BC, Canada: FriesenPress.

Women & Infants. *NICU discharge instructions*. Retrieved from http://www.womenandinfants.org/services/pregnancy/neonatal-intensive-care/nicu-discharge-instructions.cfm

Zero to Three. Retrieved from http://www.zerotothree.org

REFERENCES

Adama, E. A., Bayes, S., & Sundin, D. (2016). Parents' experiences of caring for preterm infants after discharge from neonatal intensive care unit: A meta-synthesis of the literature. *Journal of Neonatal Nursing, 22*(1), 27–51. doi:10.1016/j.jnn.2015.07.006

Affleck, G., & Tennen, H. (1991). The effect of newborn intensive care on parents' psychological well-being. *Child Health Care, 20*(1), 6–14. doi:10.1207/s15326888chc2001_2

Ahmed, A. H., & Sands, L. P. (2010). Effect of pre- and postdischarge interventions on breastfeeding outcomes and weight gain among premature infants. *Journal of Obstetric, Gynecologic, and Neonatal Nursing, 39*(1), 53–63. doi:10.1111/j.1552-6909.2009.01088.x

Allen, E. C., Manuel, J. C., Legault, C., Naughton, M. J., Pivor, C., & O'Shea, T. M. (2004). Perception of child vulnerability among mothers of former premature infants. *Pediatrics, 113*(2), 267–273. doi:10.1542/peds.113.2.267

American Academy of Pediatrics. (2010). *Early hearing detection and intervention (EHDI) guidelines for pediatric medical home providers*. Retrieved from https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/PEHDIC/Documents/Algorithm1_2010.pdf

American Academy of Pediatrics. (2014). Clinical practice guideline: The diagnosis, management, and prevention of bronchiolitis. *Pediatrics, 134*, e1474–e1502. doi:10.1542/peds.2014-2742

American Academy of Pediatrics. (2018a). Program to enhance the health and development of infants and children (PEHDIC). Retrieved from https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/PEHDIC/Pages/Early-Hearing-Detection-and-Intervention.aspx

American Academy of Pediatrics. (2018b). Recommended childhood and adolescent immunization schedules: United States, 2018. *Pediatrics, 141*(3), e20180083. doi:10.1542/peds.2018-0083

American Academy of Pediatrics. (2019). *Recommendations for preventive pediatric health care*. Retrieved from https://www.aap.org/en-us/Documents/periodicity_schedule.pdf

American Academy of Pediatrics & American College of Obstetricians and Gynecologists. (2017). *Guidelines for perinatal care* (8th ed.). Elk Grove Village, IL: Author.

American Academy of Pediatrics Committee on Fetus and Newborn. (2008). Hospital discharge of the high-risk neonate. *Pediatrics, 122*(5), 1196–1126. doi:10.1542/peds.2008-2174

American Academy of Pediatrics Early Hearing Detection and Intervention. (2018). Program to enhance the health & development of infants and children (PEHDIC). Retrieved from https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/PEHDIC/Pages/Early-Hearing-Detection-and-Intervention.aspx

Anderson, L. S., Riesch, S. K., Pridham, K. A., Lutz, K. F., & Becker, P. T. (2010). Furthering the understanding of parent–child relationships: A nursing scholarship review series. Part 4: Parent–child relationships at risk. *Journal for Specialists in Pediatric Nursing, 15*(2), 111–134. doi:10.1111/j.1744-6155.2009.00223.x

Arth, A. C., Tinker, S., Simeone, R., Ailes, E., Cragan, J., & Grosse, S. D. (2017). Inpatient hospitalization costs associated with birth defects among persons of all ages—United States, 2013. *Morbidity and Mortality Weekly Report, 66*(02), 41–46. doi:10.15585/mmwr.mm6602a1

Bagwell, G. A. (1990). *Parent transition from a special care nursery to home: A replicative study* (Master's thesis). University of Cincinnati College of Nursing, Cincinnati, OH.

Bakewell-Sachs, S., Medoff-Cooper, B., Escobar, G. J., Silber, J. H., & Lorch, S. A. (2009). Infant functional status: The timing of physiologic maturation of premature infants. *Pediatrics, 123*(5), e878–e886. doi:10.1542/peds.2008-2568

Ballantyne, M., Bernardo, S., Sozer, A., Orava, T., McPherson, A. C., Church, P., & Fehlings, D. (2018). A whole new world: A qualitative investigation of parents' experiences in transitioning their preterm child with cerebral palsy to developmental/rehabilitation services. *Developmental Neurorehabilitation, 22*(2), 87–97. doi:10.1080/17518423.2018.1434698

Ballantyne, M., Orava, T., Bernardo, S., McPherson, A. C., Church, P., & Fehlings, D. (2017). Parents' early healthcare transition experiences with preterm and acutely ill infants: A scoping review. *Child: Care, Health and Development, 43*(6), 783–796. doi:10.1111/cch.12458

Ballantyne, M., Stevens, B., Guttmann, A., Willan, A. R., & Rosenbaum, P. (2012). Transition to neonatal follow-up programs: Is attendance a problem? *Journal of Perinatal and Neonatal Nursing, 26*(1), 90–98. doi:10.1097/JPN.0b013e31823f900b

Barfield, W. D., Clements, K. M., Lee, K. G., Kotelchuck, M., Wilber, N., & Wise, P. H. (2008). Using linked data to assess patterns of early intervention (EI) referral among very low birth weight infants. *Maternal and Child Health Journal, 12*(1), 24–33. doi:10.1007/s10995-007-0227-y

Barilla, D., Marshak, H. H., Anderson, S. E., & Hopp, J. W. (2010). Postpartum follow-up: Can psychosocial support reduce newborn readmissions? *Maternal Child Nursing Journal, 35*(1), 33–39. doi:10.1097/01.NMC.0000366808.75079.cc

Barkmann, C., Helle, N., & Bindt, C. (2018). Is very low infant birth weight a predictor for a five-year course of depression in parents? A latent growth curve model. *Journal of Affective Disorders, 229*, 415–420. doi:10.1016/j.jad.2017.12.020

Barradas, D., Wasserman, M., Daniel-Robinson, L., Bruce, M., DiSantis, K., Navarro, F., . . . Goodness, B. (2016). Hospital utilization and costs among preterm infants by payer: Nationwide inpatient sample, 2009. *Maternal & Child Health Journal, 20*(4), 808–818. doi:10.1007/s10995-015-1911-y

Beck, C. T., Gable, R. K., Sakala, C., & Declercq, E. R. (2011). Postpartum depressive symptomatology: Results from a two-stage US national survey. *Journal of Midwifery and Women's Health, 56*(5), 427–435. doi:10.1111/j.1542-2011.2011.00090.x

Behrman, R. E., & Butler, A. S. (Eds.). (2007). *Preterm birth: Causes, consequences, and prevention*. Washington, DC: National Academies Press.

Benfield, D. G., Leib, S. A., & Reuter, J. (1976). Grief response of parents after referral of the critically ill newborn to a regional center. *New England Journal of Medicine, 294*(18), 975–978. doi:10.1056/NEJM197604292941803

Bergström, E.-B., Wallin, L., Thomson, G., & Flacking, R. (2012). Postpartum depression in mothers of infants cared for in a neonatal intensive care unit—Incidence and associated factors. *Journal of Neonatal Nursing, 18*(4), 143–151. doi:10.1016/j.jnn.2011.11.001

Berman, L., Raval, M. V., Ottosen, M., Mackow, A. K., Cho, M., & Goldin, A. B. (2018). Parent perspectives on readiness for discharge home after neonatal intensive care unit admission. *The Journal of Pediatrics, 205*, 98–104.e4. doi:10.1016/j.jpeds.2018.08.086

Berry, J. G., Ziniel, S. I., Freeman, L., Kaplan, W., Antonelli, R., Gay, J., . . . Goldmann, D. (2013). Hospital readmission and parent perceptions of their child's hospital discharge. *International Journal for Quality in Health Care, 25*(5), 573–581. doi:10.1093/intqhc/mzt051

Bialoskurski, M., Cox, C. L., & Hayes, J. A. (1999). The nature of attachment in a neonatal intensive care unit. *Journal of Perinatal and Neonatal Nursing, 13*(1), 66–77. doi:10.1097/00005237-199906000-00007

Bird, T. M., Bronstein, J. M., Hall, R. W., Lowery, C. L., Nugent, R., & Mays, G. P. (2010). Late preterm infants: Birth outcomes and health care utilization in the first year. *Pediatrics, 126*(2), e311–e319. doi:10.1542/peds.2009-2869

Borghini, A., Habersaat, S., Forcada-Guex, M., Nessi, J., Pierrehumbert, B., Ansermet, F., & Müller-Nix, C. (2014). Effects of an early intervention on maternal post-traumatic stress symptoms and the quality of mother–infant interaction: The case of preterm birth. *Infant Behavior and Development, 37*(4), 624–631. doi:10.1016/j.infbeh.2014.08.003

Boykova, M. (2008). Follow up care of premature babies in Russia: Evaluating parental experiences and associated services. *Infant, 4*(4), 101–105. Retrieved from http://www.infantjournal.co.uk/pdf/inf_022_xss.pdf

Boykova, M. (2016a). Life after discharge: What parents of preterm infants say about their transition to home. *Newborn and Infant Nursing Reviews, 16*(2), 58–65. doi:10.1053/j.nainr.2016.03.002

Boykova, M. (2016b). Transition from hospital to home in parents of preterm infants: A literature review. *Journal of Perinatal and Neonatal Nursing, 30*(4), 327–348. doi:10.1097/JPN.0000000000000211

Boykova, M. (2018). Transition from hospital to home in parents of preterm infants: Revision, modification, and psychometric testing of the questionnaire. *Journal of Nursing Measurement, 26*(2), 296–310. doi:10.1891/1061-3749.26.2.296

Boykova, M., & Kenner, C. (2012). Transition from hospital to home for parents of preterm infants. *Journal of Perinatal and Neonatal Nursing, 26*(1), 81–87. doi:10.1097/JPN.0b013e318243e948

Braet, A., Weltens, C., & Sermeus, W. (2016). Effectiveness of discharge interventions from hospital to home on hospital readmissions: A systematic review. *JBI Database of Systematic Reviews and Implementation Reports, 14*(2), 106–173. doi:10.11124/jbisrir-2016-2381

Brandon, D. H., Tully, K. P., Silva, S. G., Malcolm, W. F., Murtha, A. P., Turner, B. S., & Holditch-Davis, D. (2011). Emotional responses of mothers of late-preterm and term infants. *Journal of Obstetric, Gynecologic, and Neonatal Nursing, 40*(6), 719–731. doi:10.1111/j.1552-6909.2011.01290.x

Brazy, J. E., Anderson, B. M., Becker, P. T., & Becker, M. (2001). How parents of premature infants gather information and obtain support. *Neonatal Network, 20*(2), 41–48. doi:10.1891/0730-0832.20.2.41

Briere, C.-E., McGrath, J., Cong, X., & Cusson, R. (2014). An integrative review of factors that influence breastfeeding duration for premature infants after NICU hospitalization. *Journal of Obstetric, Gynecologic, and Neonatal Nursing, 43*(3), 272–281. doi:10.1111/1552-6909.12297

Brown, K. L., & Smith, L. (2018). The patient journey to home after major cardiac surgery in infancy. *Progress in Pediatric Cardiology, 48*, 8–13. doi:10.1016/j.ppedcard.2018.02.005

Browne, J. V., & Talmi, A. (2012). Developmental supports for newborns and young infants with special health and developmental needs and their families: The BABIES model. *Newborn and Infant Nursing Reviews, 12*(4), 239–247. doi:10.1053/j.nainr.2012.09.005

Burnham, N., Feeley, N., & Sherrard, K. (2013). Parents' perceptions regarding readiness for their infant's discharge from the NICU. *Neonatal Network, 32*(5), 324–334. doi:10.1891/0730-0832.32.5.324

Caplan, G., Mason, E. A., & Kaplan, D. M. (1965). Four studies of crisis in parents of prematures. *Community Mental Health Journal, 1*(2), 149–161. doi:10.1007/BF01435204

Casey, P. H. (2008). Growth of low birth weight preterm children. *Seminars in Perinatology, 32*(1), 20–27. doi:10.1053/j.semperi.2007.12.004

Chambers, P. L., Mahabee-Gittens, E. M., & Leonard, A. C. (2011). Vulnerable child syndrome, parental perception of child vulnerability, and emergency department usage. *Pediatric Emergency Care, 27*(11), 1009–1013. doi:10.1097/PEC.0b013e318235bb4f

Clements, K. M., Barfield, W. D., Ayadi, M. F., & Wilber, N. (2007). Preterm birth-associated cost of early intervention services: An analysis by gestational age. *Pediatrics, 119*(4), e866–e874. doi:10.1542/peds.2006-1729

Cook, N., Ayers, S., & Horsch, A. (2018). Maternal posttraumatic stress disorder during the perinatal period and child outcomes: A systematic review. *Journal of Affective Disorders, 225*, 18–31. doi:10.1016/j.jad.2017.07.045

Cox, C., & Bialoskurski, M. (2001). Neonatal intensive care: Communication and attachment. *British Journal of Nursing, 10*(10), 668–676. doi:10.12968/bjon.2001.10.10.9987

Crowe, S., Ridout, D., Knowles, R., Tregay, J., Wray, J., Barron, D., . . . Brown, K. (2015). Risk of death or emergency readmission following discharge after infant cardiac intervention for congenital heart disease [Abstract]. *Archives of Disease in Childhood, 100*(Suppl. 3), A71. doi:10.1136/archdischild-2015-308599.161

Crowle, C., Galea, C., Walker, K., Novak, I., & Badawi, N. (2018). Prediction of neurodevelopment at one year of age using the General Movements Assessment in the neonatal surgical population. *Early Human Development, 31*, 42–47. doi:10.1016/j.earlhumdev.2018.02.001

Currie, E. R., Christian, B. J., Hinds, P. S., Perna, S. J., Robinson, C., Day, S., & Meneses, K. (2016). Parent perspectives of neonatal intensive care at the end-of-life. *Journal of Pediatric Nursing, 31*(5), 478-489. doi:10.1016/j.pedn.2016.03.023

Currie, G., Dosani, A., Premji, S. S., Reilly, S. M., Lodha, A. K., & Young, M. (2018). Caring for late preterm infants: Public health nurses' experiences. *BMC Nursing, 17*(16), 9. doi:10.1186/s12912-018-0286-y

De Jesus, L. C., Pappas, A., Shankaran, S., Kendrick, D., Das, A., Higgins, R. D., . . . Walsh, M. C. (2012). Risk factors for post-neonatal intensive care unit discharge mortality among extremely low birth weight infants. *Journal of Pediatrics, 161*(1), 70–74. doi:10.1016/j.jpeds.2011.12.038

De Rouck, S., & Leys, M. (2009). Information needs of parents of children admitted to a neonatal intensive care unit: A review of the literature (1990–2008). *Patient Education and Counseling, 76*(2), 159–173. doi:10.1016/j.pec.2009.01.014

De Rouck, S., & Leys, M. (2011). Information behaviour of parents of children admitted to a neonatal intensive care unit: Constructing a conceptual framework. *Health, 15*(1), 54–77. doi:10.1177/1363459309360785

Delaney, A. (2018). Newborn hearing screening. In A. D. Meyers (Ed.), *Medscape*. Retrieved from https://emedicine.medscape.com/article/836646-overview#a3

Diffin, J., Spence, K., Naranian, T., Badawi, N., & Johnston, L. (2016). Stress and distress in parents of neonates admitted to the neonatal intensive care unit for cardiac surgery. *Early Human Development, 103*, 101–107. doi:10.1016/j.earlhumdev.2016.08.002

Discenza, D. (2009). NICU parents' top ten worries at discharge. *Neonatal Network, 28*(3), 202–203. doi:10.1891/0730-0832.28.3.202

Discenza, D. (2012). Preemie parent frustration: Dealing with insensitive comments. *Neonatal Network, 31*(1), 52–53. doi:10.1891/0730-0832.31.1.52

Dowling, D. A., Barsman, S. G., Forsythe, P., & Damato, E. G. (2018). Caring about Preemies' Safe Sleep (CaPSS): An educational program to improve adherence to safe sleep recommendations by mothers of preterm infants. *The Journal of Perinatal and Neonatal Nursing, 32*(4), 366–372. doi:10.1097/jpn.0000000000000345

Drake, E. (1995). Discharge teaching needs of parents in the NICU. *Neonatal Network, 14*(1), 49–53.

Eichenwald, E. C., Watterberg, K. L., Aucott, S., Benitz, W. E., Cummings, J. J., Goldsmith, J., . . . Wang, K. S. (2016). Apnea of prematurity. *Pediatrics, 137*(1), e20153757. doi:10.1542/peds.2015-3757

Ely, D. (2018). QuickStats: Infant mortality rate, by state—United States, 2016. *Morbidity and Mortality Weekly Report, 67*(33), 942. doi:10.15585/mmwr.mm6733a7

Emmanuel, E., & St John, W. (2010). Maternal distress: A concept analysis. *Journal of Advanced Nursing, 66*(9), 2104–2115. doi:10.1111/j.1365-2648.2010.05371.x

Eneriz-Wiemer, M., Liu, S.-D., Chu, M. C. Y., Uribe-Leitz, T., Rajani, K., Sankar, M., . . . Wang, C. J. (2018). Parents' knowledge and education of retinopathy of prematurity in four California neonatal intensive care units. *American Journal of Ophthalmology, 191*, 7–13. doi:10.1016/j.ajo.2018.03.039

Enke, C., Oliva y Hausmann, A., Miedaner, F., Roth, B., & Woopen, C. (2017). Communicating with parents in neonatal intensive care units: The impact on parental stress. *Patient Education and Counseling, 100*(4), 710–719. doi:10.1016/j.pec.2016.11.017

Enlow, E., Faherty, L. J., Wallace-Keeshen, S., Martin, A. E., Shea, J. A., & Lorch, S. A. (2017). Perspectives of low socioeconomic status mothers of premature infants. *Pediatrics, 139*(3), 1–8. doi:10.1542/peds.2016-2310

Epstein, E. G., Arechiga, J., Dancy, M., Simon, J., Wilson, D., & Alhusen, J. L. (2017). Integrative review of technology to support communication with parents of infants in the NICU. *Journal of Obstetric, Gynecologic and Neonatal Nursing, 46*(3), 357–366. doi:10.1016/j.jogn.2016.11.019

Feinberg, E., Donahue, S., Bliss, R., & Silverstein, M. (2012). Maternal depressive symptoms and participation in early intervention services for young children. *Maternal and Child Health Journal, 16*(2), 336–345. doi:10.1007/s10995-010-0715-3

Fierson, W. M., & American Academy of Pediatrics Section on Ophthalmology, American Academy of Ophthalmology, American Association for Pediatric Ophthalmology and Strabismus, & American Association of Certified Orthoptists. (2018). Screening examination of premature infants for retinopathy of prematurity. *Pediatrics, 142*(6), e20183061. doi:10.1542/peds.2018-3061

Flandermeyer, A., Kenner, C., Spaite, M. E., & Hostiuck, J. (1992a). Transition from hospital to home. Part II. *Neonatal Network, 11*(5), 62–63.

Flandermeyer, A., Kenner, C., Spaite, M. E., & Hostiuck, J. (1992b). Transition from hospital to home: Part III. *Neonatal Network, 11*(6), 84–85.

Fontana, C., Menis, C., Pesenti, N., Passera, S., Liotto, N., Mosca, F., . . . Fumagalli, M. (2018). Effects of early intervention on feeding behavior in preterm infants: A randomized controlled trial. *Early Human Development, 121*, 15–20. doi:10.1016/j.earlhumdev.2018.04.016

Francis, J., Unger, S., Bando, N., Vance, A., Gibbins, S., Kiss, A., . . . O'Connor, D. (2018). Post-discharge feeding of very-low-birth-weight infants: Adherence to nutrition guidelines. *Journal of Pediatric Gastroenterology and Nutrition*, *67*(3), 401–408. doi:10.1097/MPG.0000000000002041

Frawley, G. (2017). Special considerations in the premature and ex-premature infant. *Anaesthesia and Intensive Care Medicine, 18*(2), 79–83. doi:10.1016/j.mpaic.2016.11.001

Gaal, B. J., Pinelli, J., Crooks, D., Saigal, S., Streiner, D. L., & Boyle, M. (2010). Outside looking in: The lived experience of adults with prematurely born siblings. *Qualitative Health Research, 20*(11), 1532–1545. doi:10.1177/1049732310375248

Gaffney, K. F., Kitsantas, P., Brito, A., & Swamidoss, C. S. S. (2014). Postpartum depression, infant feeding practices, and infant weight gain at six months of age. *Journal of Pediatric Health Care, 28*(1), 43–50. doi:10.1016/j.pedhc.2012.10.005

Gangi, S., Dente, D., Bacchio, E., Giampietro, S., Terrin, G., & De Curtis, M. (2013). Posttraumatic stress disorder in parents of premature birth neonates. *Procedia—Social and Behavioral Sciences, 82*, 882–885. doi:10.1016/j.sbspro.2013.06.365

Garfield, C. F., Lee, Y. S., Kim, H. N., Rutsohn, J., Kahn, J. Y., Mustanski, B., & Mohr, D. C. (2016). Supporting parents of premature infants transitioning from the NICU to home: A pilot randomized control trial of a smartphone application. *Internet Interventions, 4*, 131–137. doi:10.1016/j.invent.2016.05.004

Gerstein, E. D., Njoroge, W. F. M., Paul, R. A., Smyser, C. D., & Rogers, C. E. (2019). Maternal depression and stress in the NICU: Associations with mother-child interactions at age 5 years. *Journal*

of the American Academy of Child & Adolescent Psychiatry, *58*(3), 350–358.e2. doi:10.1016/j.jaac.2018.08.016

Girgin, A. B., & Güler, C. (2017). Rehospitalization of preterm infants according to the discharge risk level. *Journal for Specialists in Pediatric Nursing, 22*(1), e12165. doi:10.1111/jspn.12165

Golish, T. D., & Powell, K. A. (2003). "Ambiguous loss": Managing the dialectics of grief associated with premature birth. *Journal of Social and Personal Relationships, 20*(3), 309–334. doi:10.1177/0265407503020003003

Gordon, J. (2009). An evidence-based approach for supporting parents experiencing chronic sorrow. *Pediatric Nursing, 35*(2), 115–119.

Goyal, N. K., Teeters, A., & Ammerman, R. T. (2013). Home visiting and outcomes of preterm infants: A systematic review. *Pediatrics, 132*(3), 502–516. doi:10.1542/peds.2013-0077

Grant, R., & Isakson, E. A. (2012). Regional variations in early intervention utilization for children with developmental delay. *Maternal and Child Health Journal, 17*(7), 1252–1259. doi:10.1007/s10995-012-1119-3

Gray, P. H., Edwards, D. M., O'Callaghan, M. J., & Cuskelly, M. (2012). Parenting stress in mothers of preterm infants during early infancy. *Early Human Development, 88*(1), 45–49. doi:10.1016/j.earlhumdev.2011.06.014

Green, M., & Solnit, A. J. (1964). Reactions to the threatened loss of a child: A vulnerable child syndrome. Pediatric management of the dying child: Part III. *Pediatrics, 34*, 58–66. Retrieved from https://pediatrics.aappublications.org/content/34/1/58

Greene, M., & Patra, K. (2016). Part C early intervention utilization in preterm infants: Opportunity for referral from a NICU follow-up clinic. *Research in Developmental Disabilities, 53–54*, 287–295. doi:10.1016/j.ridd.2016.02.016

Greene, M. M., Rossman, B., Meier, P., & Patra, K. (2017). Parental perception of child vulnerability among mothers of very low birth weight infants: Psychological predictors and neurodevelopmental sequelae at 2 years. *Journal of Perinatology, 37*(4), 454–460. doi:10.1038/jp.2016.197

Grosse, S. D., Waitzman, N. J., Yang, N., Abe, K., & Barfield, W. (2017). Employer-sponsored plan expenditures for infants born preterm. *Pediatrics, 140*(4), e20171078. doi:10.1542/peds.2017-1078

Gullino, S., Kaiser, A., Khan, H., Phillips, A., Elwin, A., & Edwards, A. D. (2017). New mothers' experiences of the urban environment with their preterm infants involve complex social, emotional and psychological processes. *Acta Pædiatrica, 106*(3), 405–410. doi:10.1111/apa.13715

Hall, R. A. S., Hoffenkamp, H. N., Braeken, J., Tooten, A., Vingerhoets, A. J. J. M., & van Bakel, H. J. A. (2017). Maternal psychological distress after preterm birth: Disruptive or adaptive? *Infant Behavior and Development, 49*, 272–280. doi:10.1016/j.infbeh.2017.09.012

Harris, R., Gibbs, D., Mangin-Heimos, K., & Pineda, R. (2018). Maternal mental health during the neonatal period: Relationships to the occupation of parenting. *Early Human Development, 120*, 31–39. doi:10.1016/j.earlhumdev.2018.03.009

Harron, K., Gilbert, R., Cromwell, D., Oddie, S., & van der Meulen, J. (2017). Newborn length of stay and risk of readmission. *Paediatric and Perinatal Epidemiology, 31*(3), 221–232. doi:10.1111/ppe.12359

Helle, N., Barkmann, C., Ehrhardt, S., & Bindt, C. (2018). Postpartum posttraumatic and acute stress in mothers and fathers of infants with very low birth weight: Cross-sectional results from a controlled multicenter cohort study. *Journal of Affective Disorders, 235*, 467–473. doi:10.1016/j.jad.2018.04.013

Hess, C. R., Teti, D. M., & Hussey-Gardner, B. (2004). Self-efficacy and parenting of high-risk infants: The moderating role of parent knowledge of infant development. *Journal of Applied Developmental Psychology, 25*(4), 423–437. doi:10.1016/j.appdev.2004.06.002

Holditch-Davis, D., Miles, M. S., Burchinal, M. R., & Goldman, B. D. (2011). Maternal role attainment with medically fragile infants: Part 2: Relationship to the quality of parenting. *Research in Nursing and Health, 34*(1), 35–48. doi:10.1002/nur.20418

Holditch-Davis, D., Miles, M. S., Weaver, M. A., Black, B., Beeber, L., Thoyre, S., & Engelke, S. (2009). Patterns of distress in African-American mothers of preterm infants. *Journal of Developmental and Behavioral Pediatrics, 30*(3), 193–205. doi:10.1097/DBP.0b013e3181a7ee53

Holditch-Davis, D., Santos, H., Levy, J., White-Traut, R., O'Shea, T. M., Geraldo, V., & David, R. (2015). Patterns of psychological distress in mothers of preterm infants. *Infant Behavior and Development, 41*, 154–163. doi:10.1016/j.infbeh.2015.10.004

Hollywood, M., & Hollywood, E. (2011). The lived experiences of fathers of a premature baby on a neonatal intensive care unit. *Journal of Neonatal Nursing, 17*(1), 32–40. doi:10.1016/j.jnn.2010.07.015

Holte, L., Walker, E., Oleson, J., Spratford, M., Moeller, M., Roush, P., . . . Ou, H. (2012). Factors influencing follow-up to newborn hearing screening for infants who are hard of hearing. *American Journal of Audiology, 21*(2), 163–174. doi:10.1044/1059-0889(2012/12-0016)

Hymas, R., & Girard, L.-C. (2018). Predicting postpartum depression among adolescent mothers: A systematic review of risk. *Journal of Affective Disorders, 246*, 873–885. doi:10.1016/j.jad.2018.12.041

Hynan, M. T. (2016). The transformation of the neonatal intensive care unit: A father's perspective over 36 years. *Newborn and Infant Nursing Reviews, 16*(4), 285–288. doi:10.1053/j.nainr.2016.09.021

Ireland, J., Minesh, K., Cescutti-Butler, L., van Teijlingen, E., & Hewitt-Taylor, J. (2016). Experiences of fathers with babies admitted to neonatal care units: A review of the literature. *Journal of Neonatal Nursing, 22*(4), 171–176. doi:10.1016/j.jnn.2016.01.006

Johnson, S., & Marlow, N. (2017). Early and long-term outcome of infants born extremely preterm. *Archives of Disease in Childhood, 102*, 97–102. doi:10.1136/archdischild-2015-309581

Jones, L., Rowe, J., & Becker, T. (2009). Appraisal, coping, and social support as predictors of psychological distress and parenting efficacy in parents of premature infants. *Children's Health Care, 38*(4), 245–262. doi:10.1080/02739610903235976

Jubinville, J., Newburn-Cook, C., Hegadoren, K., & Lacaze-Masmonteil, T. (2012). Symptoms of acute stress disorder in mothers of premature infants. *Advances in Neonatal Care, 12*(4), 246–253. doi:10.1097/ANC.0b013e31826090ac

Kallem, S., Matone, M., Boyd, R. C., & Guevara, J. P. (2018). Mothers' mental health care utilization after screening for postpartum depression at well child visits. *Academic Pediatrics*. Advance online publication. doi:10.1016/j.acap.2018.11.013

Kenner, C. (1988). *Parent transition from newborn intensive care unit to home.* (Doctoral dissertation). Indiana University, Indianapolis, IN. Retrieved from http://openlibrary.org/works/OL2733775W/PARENT_TRANSITION_FROM_THE_NEWBORN_INTENSIVE_CARE_UNIT_(NICU)_TO_HOME

Kenner, C. (1990). Caring for the NICU parent. *Journal of Perinatal and Neonatal Nursing, 4*(3), 78–87. doi:10.1097/00005237-199012000-00010

Kenner, C., & Lott, J. W. (1990). Parent transition after discharge from the NICU. *Neonatal Network, 9*(2), 31–37.

Kersting, A., Dorsch, M., Wesselmann, U., Lüdorff, K., Witthaut, J., Ohrmann, P., . . . Arolt, V. (2004). Maternal posttraumatic stress response after the birth of a very low-birth-weight infant. *Journal of Psychosomatic Research, 57*(5), 473–476. doi:10.1016/j.jpsychores.2004.03.011

Kim, H. N. (2018). Social support provision: Perspective of fathers with preterm infants. *Journal of Pediatric Nursing, 39*, 44–48. doi:10.1016/j.pedn.2018.01.017

Kirkby, S., Greenspan, J., Kornhauser, M., & Schneiderman, R. (2007). Clinical outcomes and cost of the moderately preterm infant. *Advances in Neonatal Care, 7*(2), 80–87. doi:10.1097/01.ANC.0000267913.58726.f3

Klein, L. (2011). Effectiveness of parent education on late preterm infants' readmission rates. *Journal of Obstetric, Gynecologic, and Neonatal Nursing, 40*(Suppl. 1), S110–S111. doi:10.1111/j.1552-6909.2011.01243_31.x

Kokotos, F., & Adam, H. M. (2009). The vulnerable child syndrome. *Pediatrics in Review, 30*(5), 193–194. doi:10.1542/pir.30-5-193

Korja, R., Latva, R., & Lehtonen, L. (2012). The effects of preterm birth on mother–infant interaction and attachment during the infant's first

two years. *Acta Obstetricia et Gynecologica Scandinavica, 91*(2), 164–173. doi:10.1111/j.1600-0412.2011.01304.x

Kowalski, W. J., Leef, K. H., Mackley, A., Spear, M. L., & Paul, D. A. (2006). Communicating with parents of premature infants: Who is the informant? *Journal of Perinatology, 26*(1), 44–48. doi:10.1038/sj.jp.7211409

Kripalani, S., LeFevre, F., Phillips, C. O., Williams, M. V., Basaviah, P., & Baker, D. W. (2007). Deficits in communication and information transfer between hospital-based and primary care physicians: Implications for patient safety and continuity of care. *Journal of the American Medical Association, 297*(8), 831–841. doi:10.1001/jama.297.8.831

Kuzniewicz, M. W., Parker, S.-J., Schnake-Mahl, A., & Escobar, G. J. (2013). Hospital readmissions and emergency department visits in moderate preterm, late preterm, and early term infants. *Clinics in Perinatology, 40*(4), 753–775. doi:10.1016/j.clp.2013.07.008

LaHood, A., & Bryant, C. A. (2007). Outpatient care of the premature infant. *American Family Physician, 76*(8), 1159–1164. Retrieved from https://www.aafp.org/afp/2007/1015/p1159.html

Lakshmanan, A., Agni, M., Lieu, T., Fleegler, E., Kipke, M., Friedlich, P. S., . . . Belfort, M. B. (2017). The impact of preterm birth <37 weeks on parents and families: A cross-sectional study in the 2 years after discharge from the intensive care unit. *Health and Quality of Life Outcomes, 15*, 38. doi:10.1186/s12955-017-0602-3

Levy, J. C. (1980). Vulnerable children: Parents' perspectives and the use of medical care. *Pediatrics, 65*(5), 956–963. Retrieved from https://pediatrics.aappublications.org/content/65/5/956

Lindberg, B., Axelsson, K., & Öhrling, K. (2009). Taking care of their baby at home but with nursing staff as support: The use of videoconferencing in providing neonatal support to parents of preterm infants. *Journal of Neonatal Nursing, 15*(2), 47–55. doi:10.1016/j.jnn.2009.01.004

Litt, J. S., Glymour, M. M., Hauser-Cram, P., Hehir, T., & McCormick, M. C. (2018). Early intervention services improve school-age functional outcome among neonatal intensive care unit graduates. *Academic Pediatrics, 18*(4), 468–474. doi:10.1016/j.acap.2017.07.011

Little, A. A., Kamholz, K., Corwin, B. K., Barrero-Castillero, A., & Wang, C. J. (2015). Understanding barriers to early intervention services for preterm infants: Lessons from two states. *Academic Pediatrics, 15*(4), 430–438. doi:10.1016/j.acap.2014.12.006

Liu, C. L., Farrell, J., MacNeil, J. R., Stone, S., & Barfield, W. (2008). Evaluating loss to follow-up in newborn hearing screening in Massachusetts. *Pediatrics, 121*(2), e335–e343. doi:10.1542/peds.2006-3540

Liu, Y., McGowan, E., Tucker, R., Glasgow, L., Kluckman, M., & Vohr, B. (2018). Transition Home Plus Program reduces Medicaid spending and health care use for high-risk infants admitted to the neonatal intensive care unit for 5 or more days. *Journal of Pediatrics, 200*, 91–97. doi:10.1016/j.jpeds.2018.04.038

Loo, K. K., Espinosa, M., Tyler, R., & Howard, J. (2003). Using knowledge to cope with stress in the NICU: How parents integrate learning to read the physiologic and behavioral cues of the infant. *Neonatal Network, 22*(1), 31–37. doi:10.1891/0730-0832.22.1.31

Lorch, S. A., Srinivasan, L., & Escobar, G. J. (2011). Epidemiology of apnea and bradycardia resolution in premature infants. *Pediatrics, 128*(2), e366–e373. doi:10.1542/peds.2010-1567

Lundeen, E. C. (1937). The premature infant at home. *American Journal of Nursing, 37*, 466–470. Retrieved from https://journals.lww.com/ajnonline/Fulltext/1937/05000/The_Premature_Infant_at_Home.3.aspx

Lutz, K. F. (2012). Feeding problems of neonatal intensive care unit and pediatric intensive care unit graduates: Perceptions of parents and providers. *Newborn and Infant Nursing Reviews, 12*(4), 207–213. doi:10.1053/j.nainr.2012.09.008

Lutz, K. F., Anderson, L. S., Riesch, S. K., Pridham, K. A., & Becker, P. T. (2009). Furthering the understanding of parent-child relationships: A nursing scholarship review series. Part 2: Grasping the early parenting experience--the insider view. *Journal for Specialists in Pediatric Nursing, 14*(4), 262–283. doi:10.1111/j.1744-6155.2009.00209.x

Mackie, A. S., Ionescu-Ittu, R., Pilote, L., Rahme, E., & Marelli, A. J. (2008). Hospital readmissions in children with congenital heart disease: A population-based study. *American Heart Journal, 155*(3), 577–584. doi:10.1016/j.ahj.2007.11.003

Mackley, A. B., Locke, R. G., Spear, M. L., & Joseph, R. (2010). Forgotten parent: NICU paternal emotional response. *Advances in Neonatal Care, 10*(4), 200–203. doi:10.1097/ANC.0b013e3181e946f0

Makaryus, A. N., & Friedman, E. A. (2005). Patients' understanding of their treatment plans and diagnosis at discharge. *Mayo Clinic Proceedings, 80*(8), 991–994. doi:10.4065/80.8.991

Mäkelä, H., Axelin, A., Feeley, N., & Niela-Vilén, H. (2018). Clinging to closeness: The parental view on developing a close bond with their infants in a NICU. *Midwifery, 62*, 183–188. doi:10.1016/j.midw.2018.04.003

May, K. M. (1997). Searching for normalcy: Mothers' caregiving for low birth weight infants. *Pediatric Nursing, 23*(1), 17–20.

McIntyre, S., Morgan, C.,Walker, K., & Novak, I. (2011). Cerebral palsy—Don't delay. *Developmental Disabilities Research Reviews, 17*(2), 114–1129. doi:10.1002/ddrr.1106

McKim, E. (1993). The information and support needs of mothers of premature infants. *Journal of Pediatric Nursing, 8*(4), 233–244. Retrieved from https://www.pediatricnursing.org/article/0882-5963(93)90094-2/pdf

McKim, E., Kenner, C., Flandermeyer, A., Spangler, L., Darling-Thornburg, P., & Spiering, K. (1995). The transition to home for mothers of healthy and initially ill newborn babies. *Midwifery, 11*(4), 184–194. doi:10.1016/0266-6138(95)90003-9

McLaurin, K., Wade, S., Farr, A., & Franklin, J. (2017). Medicaid and commercially insured preterm births in the United States. *Pediatrics, 140*(1), 72. doi:10.1542/peds.140.1_MeetingAbstract.72

McLaurin, K. K., Hall, C. B., Jackson, E. A., Owens, O. V., & Mahadevia, P. J. (2009). Persistence of morbidity and cost differences between late-preterm and term infants during the first year of life. *Pediatrics, 123*(2), 653–659. doi:10.1542/peds.2008-1439

McManus, B., McCormick, M. C., Acevedo-Garcia, D., Ganz, M., & Hauser-Cram, P. (2009). The effect of state early intervention eligibility policy on participation among a cohort of young CSHCN. *Pediatrics, 124*(Suppl. 4), S368–S374. doi:10.1542/peds.2009-1255G

McManus, B. M., & Poehlmann, J. (2012). Parent–child interaction, maternal depressive symptoms and preterm infant cognitive function. *Infant Behavior and Development, 35*(3), 489–498. doi:10.1016/j.infbeh.2012.04.005

Melnyk, B. M., Bullock, T., McGrath, J., Jacobson, D., Kelly, S., & Baba, L. (2010). Translating the evidence-based NICU COPE program for parents of premature infants into clinical practice: Impact on nurses' evidence-based practice and lessons learned. *The Journal of Perinatal and Neonatal Nursing, 24*(1), 74–80 doi:10.1097/JPN.0b013e3181ce314b

Melnyk, B. M., Crean, H. F., Feinstein, N. F., & Fairbanks, E. (2008). Maternal anxiety and depression after a premature infant's discharge from the neonatal intensive care unit: Explanatory effects of the Creating Opportunities for Parent Empowerment program. *Nursing Research, 57*(6), 383–394. doi:10.1097/NNR.0b013e3181906f59

Melnyk, B. M., & Feinstein, N. F. (2009). Reducing hospital expenditures with the COPE (Creating Opportunities for Parent Empowerment) program for parents and premature infants: An analysis of direct healthcare neonatal intensive care unit costs and savings. *Nursing Administration Quarterly, 33*(1), 32–37. doi:10.1097/01.NAQ.0000343346.47795.13

Mercer, R. T. (1995). *Becoming a mother: Research on maternal identity from Rubin to the present*. New York, NY: Springer Publishing Company.

Mercer, R. T. (2004). Becoming a mother versus maternal role attainment. *Journal of Nursing Scholarship, 36*(3), 226–232. doi:10.1111/j.1547-5069.2004.04042.x

Mercer, R. T., & Walker, L. O. (2006). A review of nursing interventions to foster becoming a mother. *Journal of Obstetric, Gynecologic and Neonatal Nursing, 35*(5), 568–582. doi:10.1111/j.1552-6909.2006.00080.x

Mew, A. M., Holditch-Davis, D., Belyea, M., Miles, M. S., & Fishel, A. (2003). Correlates of depressive symptoms in

mothers of preterm infants. *Neonatal Network, 22*(5), 51–60. doi:10.1891/0730-0832.22.5.51

Miles, M. S., Funk, S. G., & Kasper, M. A. (1992). The stress response of mothers and fathers of preterm infants. *Research in Nursing and Health, 15*(4), 261–269. doi:10.1002/nur.4770150405

Miles, M. S., & Holditch-Davis, D. (1995). Compensatory parenting: How mothers describe parenting their 3-year-old, prematurely born children. *Journal of Pediatric Nursing, 10*(4), 243–253. doi:10.1016/S0882-5963(05)80021-1

Miles, M. S., & Holditch-Davis, D. (1997). Parenting the prematurely born child: Pathways of influence. *Seminars in Perinatology, 21*(3), 254–266. doi:10.1016/S0146-0005(97)80067-5

Miles, M. S., Holditch-Davis, D., Burchinal, M. R., & Brunssen, S. (2011). Maternal role attainment with medically fragile infants: Part 1. Measurement and correlates during the first year of life. *Research in Nursing and Health, 34*(1), 20–34. doi:10.1002/nur.20419

Miller, B. C., & Sollie, D. L. (1980). Normal stresses during the transition to parenthood. *Family Relations, 29*(4), 459–465. doi:10.2307/584459

Montenegro, B. L., Amberson, M., Veit, L., Freiberger, C., Dukhovny, D., & Rhein, L. M. (2017). Economics of home monitoring for apnea in late preterm infants. *Respiratory Care, 62*(1), 42–48. doi:10.4187/respcare.04954

Morrison, A., & Gullón-Rivera, A. L. (2017). Supporting siblings of neonatal intensive care unit patients: A NICU social story™ as an innovative approach. *Journal of Pediatric Nursing, 33*, 91–93. doi:10.1016/j.pedn.2016.12.002

Mowery, B. D. (2011). Post-traumatic stress disorder (PTSD) in parents: Is this a significant problem? *Pediatric Nursing, 37*(2), 89–92.

Munoz, K., Nelson, L., Goldgewicht, N., & Odell, D. (2011). Early hearing detection and intervention: Diagnostic hearing assessment practices. *American Journal of Audiology, 20*(2), 123–131. doi:10.1044/1059-0889(2011/10-0046)

Murch, T. N., & Smith, V. C. (2016). Supporting families as they transition home. *Newborn and Infant Nursing Reviews, 16*(4), 298–302. doi:10.1053/j.nainr.2016.09.024

Navar-Boggan, A. M., Halsey, N. A., Escobar, G. J., Golden, W. C., & Klein, N. P. (2011). Underimmunization at discharge from the neonatal intensive care unit. *Journal of Perinatology, 32*, 363–367. doi:10.1038/jp.2011.111

Naylor, M. D., Aiken, L. H., Kurtzman, E. T., Olds, D. M., & Hirschman, K. B. (2011). The care span: The importance of transitional care in achieving health reform. *Health Affairs, 30*(4), 746–754. doi:10.1377/hlthaff.2011.0041

Naylor, M. D., Bowles, K. H., McCauley, K. M., Maccoy, M. C., Maislin, G., Pauly, M. V., & Krakauer, R. (2011). High-value transitional care: Translation of research into practice. *Journal of Evaluation in Clinical Practice, 19*(5), 727–733. doi:10.1111/j.1365-2753.2011.01659.x

Naylor, M. D., Brooten, D. A., Campbell, R. L., Maislin, G., McCauley, K. M., & Schwartz, J. S. (2004). Transitional care of older adults hospitalized with heart failure: A randomized, controlled trial. *Journal of the American Geriatrics Society, 52*(5), 675–684. doi:10.1111/j.1532-5415.2004.52202.x

Naylor, M. D., Feldman, P. H., Keating, S., Koren, M. J., Kurtzman, E. T., Maccoy, M. C., & Krakauer, R. (2009). Translating research into practice: Transitional care for older adults. *Journal of Evaluation in Clinical Practice, 15*(6), 1164–1170. doi:10.1111/j.1365-2753.2009.01308.x

Noergaard, B., Ammentorp, J., Garne, E., Fenger-Gron, J., & Kofoed, P. E. (2018). Fathers' stress in a neonatal intensive care unit. *Advances in Neonatal Care, 18*(5), 1. doi:10.1097/ANC.0000000000000503

Novak, I., Hines, M. E., Goldsmith, S., & Barclay, R. (2012). Clinical prognostic messages from a systematic review on cerebral palsy. *Pediatrics, 130*(5), e1285–e1312. doi:10.1542/peds.2012-0924

Novak, I., Morgan, C., Adde, L., Blackman, J., Boyd, R. N., Brunstrom-Hernandez, J., . . . Badawi, N. (2017). Early, accurate diagnosis and early intervention in cerebral palsy: Advances in diagnosis and treatment. *JAMA Pediatrics, 171*(9), 897–907. doi:10.1001/jamapediatrics.2017.1689

Obregon, E., Martin, C. R., Frantz Iii, I. D., Patel, P., & Smith, V. C. (2019). Neonatal intensive care unit discharge preparedness among families with limited English proficiency. *Journal of Perinatology, 39*(1), 135–142. doi:10.1038/s41372-018-0255-z

Padovani, F. H. P., Carvalho, A. E. V., Duarte, G., Martinez, F. E. M., & Linhares, M. B. M. (2009). Anxiety, dysphoria, and depression symptoms in mothers of preterm infants. *Psychological Reports, 104*(2), 667–679. doi:10.2466/pr0.104.2.667-679

Peters, T., & Pompeii-Wolfe, C. (2018). Nutrition considerations after NICU discharge. *Pediatric Annals, 47*(4), e154–e158. doi:10.3928/19382359-20180327-02

Placencia, F. X., & McCullough, L. B. (2012). Biopsychosocial risks of parental care for high-risk neonates: Implications for evidence-based parental counseling. *Journal of Perinatology, 32*(5), 381–386. doi:10.1038/jp.2011.109

Pritchard, M. A., Colditz, P. B., & Beller, E. M. (2008). Parental experiences and preferences which influence subsequent use of post-discharge health services for children born very preterm. *Journal of Paediatrics and Child Health, 44*(5), 281–284. doi:10.1111/j.1440-1754.2007.01256.x

Prouhet, P. M., Gregory, M. R., Russell, C. L., & Yaeger, L. H. (2018). Fathers' stress in the neonatal intensive care unit: A systematic review. *Advances in Neonatal Care, 18*(2), 105–120. doi:10.1097/ANC.0000000000000472

Purdy, I. B., & Melwak, M. A. (2012). Who is at risk? High-risk infant follow-up. *Newborn and Infant Nursing Reviews, 12*(4), 221–226. doi:10.1053/j.nainr.2012.09.011

Purdy, I. B., Melwak, M. A., Smith, J. R., Kenner, C., Chuffo-Siewert, R., Ryan, D. J., …Hall, S. (2017). Neonatal nurses NICU quality improvement: Embracing EBP recommendations to provide parent psychosocial support. *Advances in Neonatal Care, 17*(1), 33–44. doi:10.1097/ANC.0000000000000352

Radecki, L., Olson, L. M., Frintner, M. P., Tanner, J. L., & Stein, M. T. (2009). What do families want from well-child care? Including parents in the rethinking discussion. *Pediatrics, 124*(3), 858–865. doi:10.1542/peds.2008-2352

Raines, D. A. (2013). Mothers' stressor as the day of discharge from the NICU approaches. *Advances in Neonatal Care, 13*(3), 181–187. doi:10.1097/ANC.0b013e318285fa2a

Ralser, E., Mueller, W., Haberland, C., Fink, F.-M., Gutenberger, K.-H., Strobl, R., & Kiechl-Kohlendorfer, U. (2012). Rehospitalization in the first 2 years of life in children born preterm. *Acta Pædiatrica, 101*(1), e1–e5. doi:10.1111/j.1651-2227.2011.02404.x

Rautava, P., Lehtonen, L., Helenius, H., & Sillanpaa, M. (2003). Effect of newborn hospitalization on family and child behavior: A 12-year follow-up study. *Pediatrics, 111*(2), 277–283. doi:10.1542/peds.111.2.277

Ray, K. N., Escobar, G. J., & Lorch, S. A. (2010). Premature infants born to adolescent mothers: Health care utilization after initial discharge. *Academic Pediatrics, 10*(5), 302–308. doi:10.1016/j.acap.2010.07.005

Rogers, C. E., Kidokoro, H., Wallendorf, M., & Inder, T. E. (2013). Identifying mothers of very preterm infants at-risk for postpartum depression and anxiety before discharge. *Journal of Perinatology, 33*(3), 171–176. doi:10.1038/jp.2012.75

Rose, L., Herzig, L. D., & Hussey-Gardner, B. (2014). Early intervention and the role of pediatricians. *Pediatrics in Review, 35*(1), e1–e10. doi:10.1542/pir.35-1-e1

Rosenbaum, P., Paneth, N., Leviton, A., Goldstein, M., Bax, M., Damiano, D., & Jacobsson, B. (2007). A report: The definition and classification of cerebral palsy April 2006. *Developmental Medicine & Child Neurology, 49*(6), 8–14. doi:10.1111/j.1469-8749.2007.00201.x

Ross, E. S., & Browne, J. V. (2013). Feeding outcomes in preterm infants after discharge from the neonatal intensive care unit (NICU): A systematic review. *Newborn and Infant Nursing Reviews, 13*(2), 87–93. doi:10.1053/j.nainr.2013.04.003

Rubin, R. (1984). *Maternal identity and the maternal experience*. New York, NY: Springer Publishing Company.

Saigal, S., Pinelli, J., Streiner, D. L., Boyle, M., & Stoskopf, B. (2010). Impact of extreme prematurity on family functioning and maternal health 20 years later. *Pediatrics, 126*(1), e81–e88. doi:10.1542/peds.2009-2527

Sanchez, K., Spittle, A. J., Slattery, J. M., & Morgan, A. T. (2016). Oromotor feeding in children born before 30 weeks' gestation and

term-born peers at 12 months' corrected age. *Journal of Pediatrics, 178*, 113–118.e111. doi:10.1016/j.jpeds.2016.07.044

Seideman, R. Y., Watson, M. A., Corff, K. E., Odle, P., Haase, J., & Bowerman, J. L. (1997). Parent stress and coping in NICU and PICU. *Journal of Pediatric Nursing, 12*(3), 169–177. doi:10.1016/s0882-5963(97)80074-7

Shah, P. E., Clements, M., & Poehlmann, J. (2011). Maternal resolution of grief after preterm birth: Implications for infant attachment security. *Pediatrics, 127*(2), 284–292. doi:10.1542/peds.2010-1080

Shakeel, F. (2016). *Post-discharge nutrition in preterm infant*. Retrieved from https://www.hopkinsallchildrens.org/getmedia/2ad32c9c-c5e0-42e3-baf8-0b8c11286035/2016-10-28_PGR_Shakeel.pdf

Shaw, R. J., Bernard, R. S., Deblois, T., Ikuta, L. M., Ginzburg, K., & Koopman, C. (2009). The relationship between acute stress disorder and posttraumatic stress disorder in the neonatal intensive care unit. *Psychosomatics, 50*(2), 131–137. doi:10.1176/appi.psy.50.2.131

Sherman, M. P., Lauriello, N. F., & Aylward, G. P. (2016). Follow-up of the NICU patient. In T. Rosenkrantz (Ed.), *Medscape*. Retrieved from http://emedicine.medscape.com/article/1833812-overview

Sloan, K., Rowe, J., & Jones, L. (2008). Stress and coping in fathers following the birth of a preterm infant. *Journal of Neonatal Nursing, 14*(4), 108–115. doi:10.1016/j.jnn.2007.12.009

Smith, V. C., Dukhovny, D., Zupancic, J. A., Gates, H. B., & Pursley, D. M. (2012). Neonatal intensive care unit discharge preparedness: Primary care implications. *Clinical Pediatrics, 51*, 454–461. doi:10.1177/0009922811433036

Smith, V. C., Young, S., Pursley, D. M., McCormick, M. C., & Zupancic, J. A. (2009). Are families prepared for discharge from the NICU? *Journal of Perinatology, 29*(9), 623–629. doi:10.1038/jp.2009.58

Smithers-Sheedy, H., McIntyre, S., Gibson, C., Meehan, E., Scott, H., Goldsmith, S., . . . Blair, E. (2016). A special supplement: Findings from the Australian Cerebral Palsy Register, birth years 1993 to 2006. *Developmental Medicine & Child Neurology, 58*, 5–10. doi:10.1111/dmcn.13026

Sneath, N. (2009). Discharge teaching in the NICU: Are parents prepared? An integrative review of parents' perceptions. *Neonatal Network, 28*(4), 237–246. doi:10.1891/0730-0832.28.4.237

South, A. P., Wessel, J. J., Sberna, A., Patel, M., & Morrow, A. L. (2011). Hospital readmission among infants with gastroschisis. *Journal of Perinatology, 31*(8), 546–550. doi:10.1038/jp.2010.206

Spangler-Torok, L. (2001). Maternal perceptions of the technology-dependent infant (Doctoral dissertation). Cincinnati, OH: University of Cincinnati.

Spicer, A., Pinelli, J., Saigal, S., Wu, Y. W., Cunningham, C., & DiCenso, A. (2008). Health status and health service utilization of infants and mothers during the first year after neonatal intensive care. *Advances in Neonatal Care, 8*(1), 33–41. doi:10.1097/01.ANC.0000311015.56263.6f

Spiegler, J., Schlaud, M., König, I. R., Teig, N., Hubert, M., Herting, E., & Göpel, W. (2013). Very low birth weight infants after discharge: What do parents describe? *Early Human Development, 89*(5), 343–347. doi:10.1016/j.earlhumdev.2012.11.007

Spinelli, M., Frigerio, A., Montali, L., Fasolo, M., Spada, M. S., & Mangili, G. (2015). "I still have difficulties feeling like a mother": The transition to motherhood of preterm infants mothers. *Psychology and Health, 31*(2), 184–204. doi:10.1080/08870446.2015.1088015

Spittle, A. J. O., Anderson, P. J., Boyd, R., & Doyle, L. W. (2015). Early developmental intervention programmes provided posthospital discharge to prevent motor and cognitive impairment in preterm infants (review). *Cochrane Database of Systematic Reviews*, (11), CD005495. doi:10.1002/14651858.CD005495.pub4

Spittle, A., & Treyvaud, K. (2016). The role of early developmental intervention to influence neurobehavioral outcomes of children born preterm. *Seminars in Perinatology, 40*(8), 542–548. doi:10.1053/j.semperi.2016.09.006

Tallandini, M. A., Morsan, V., Gronchi, G., & Macagno, F. (2015). Triggering agents of parental perception of child's vulnerability in instances of preterm birth: A systematic and meta-analytic review. *Journal of Pediatric Psychology, 40*(6), 545–553. doi:10.1093/jpepsy/jsv010

Tang, B. G., Feldman, H. M., Huffman, L. C., Kagawa, K. J., & Gould, J. B. (2012). Missed opportunities in the referral of high-risk infants to early intervention. *Pediatrics, 129*(6), 1027–1034. doi:10.1542/peds.2011-2720

Teller, I. C., Embleton, N. D., Griffin, I. J., & van Elburg, R. M. (2016). Post-discharge formula feeding in preterm infants: A systematic review mapping evidence about the role of macronutrient enrichment. *Clinical Nutrition, 35*(4), 791–801. doi:10.1016/j.clnu.2015.08.006

Teti, D. M., Hess, C. R., & O'Connell, M. (2005). Parental perceptions of infant vulnerability in a preterm sample: Prediction from maternal adaptation to parenthood during the neonatal period. *Journal of Developmental and Behavioral Pediatrics, 26*(4), 283–292. doi:10.1097/00004703-200508000-00004

Tomlin, A. M., Deloian, B., & Wollesen, L. (2016). Infant/early childhood mental health and collaborative partnerships: Beyond the NICU. *Newborn and Infant Nursing Reviews, 16*(4), 309–315. doi:10.1053/j.nainr.2016.09.025

Toral-López, I., Fernández-Alcántara, M., González-Carrión, P., Cruz-Quintana, F., Rivas-Campos, A., & Pérez-Marfil, N. (2016). Needs perceived by parents of preterm infants: Integrating care into the early discharge process. *Journal of Pediatric Nursing, 31*(2), e99–e108. doi:10.1016/j.pedn.2015.09.007

Torchin, H., Rousseau, J., Marchand-Martin, L., Truffert, P., Jarreau, P. H., & Ancel, P. Y. (2018). Palivizumab administration in preterm infants in France: EPIPAGE-2 cohort study. *Archives de Pédiatrie, 25*(2), 89–94. doi:10.1016/j.arcped.2017.12.009

Tregay, J., Brown, K. L., Crowe, S., Bull, C., Knowles, R. L., Smith, L., & Wray, J. (2016). Signs of deterioration in infants discharged home following congenital heart surgery in the first year of life: A qualitative study. *Archives of Disease in Childhood, 101*(10), 902. doi:10.1136/archdischild-2014-308092

Treherne, S. C., Feeley, N., Charbonneau, L., & Axelin, A. (2017). Parents' perspectives of closeness and separation with their preterm infants in the NICU. *Journal of Obstetric, Gynecologic and Neonatal Nursing, 46*(5), 737–747. doi:10.1016/j.jogn.2017.07.005

Underwood, M. A., Danielsen, B., & Gilbert, W. M. (2007). Cost, causes and rates of rehospitalization of preterm infants. *Journal of Perinatology, 27*(10), 614–619. doi:10.1038/sj.jp.7211801

Usatin, D., Liljestrand, P., Kuzniewicz, M. W., Escobar, G. J., & Newman, T. B. (2010). Effect of neonatal jaundice and phototherapy on the frequency of first-year outpatient visits. *Pediatrics, 125*(4), 729–734. doi:10.1542/peds.2009-0172

U.S. Department of Education. (2011). *Individuals with Disabilities Act of 2011, Stat.303*. Retrieved from https://sites.ed.gov/idea/regs/c/a/303.13

Valizadeh, L., Zamanzadeh, V., & Rahiminia, E. (2012). Comparison of anticipatory grief reaction between fathers and mothers of premature infants in neonatal intensive care unit. *Scandinavian Journal of Caring Sciences, 27*(4), 921–926. doi:10.1111/scs.12005

Vazquez, V., & Cong, X. (2014). Parenting the NICU infant: A meta-ethnographic synthesis. *International Journal of Nursing Sciences, 1*(3), 281–290. doi:10.1016/j.ijnss.2014.06.001

Villar, J., Cheikh Ismail, L., Victora, C. G., Ohuma, E. O., Bertino, E., Altman, D. G., . . . Kennedy, S. H. (2014). International standards for newborn weight, length, and head circumference by gestational age and sex: The Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. *Lancet, 384*(9946), 857–868. doi:10.1016/S0140-6736(14)60932-6

Vohr, B. R. (2016). Language and hearing outcomes of preterm infants. *Seminars in Perinatology, 40*(8), 510–519. doi:10.1053/j.semperi.2016.09.003

Wade, K. C., Lorch, S. A., Bakewell-Sachs, S., Medoff-Cooper, B., Silber, J. H., & Escobar, G. J. (2008). Pediatric care for preterm infants after NICU discharge: High number of office visits and prescription medications. *Journal of Perinatology, 28*, 696–701. doi:10.1038/jp.2008.74

Walker, K., Holland, A. J., Halliday, R., & Badawi, N. (2012). Which high-risk infants should we follow-up and how should we do it? *Journal of Paediatrics and Child Health, 48*(9), 789–793. doi:10.1111/j.1440-1754.2012.02540.x

Wang, C. J., Elliott, M. N., McGlynn, E. A., Brook, R. H., & Schuster, M. A. (2008). Population-based assessments of ophthalmologic and audiologic follow-up in children with very low birth weight enrolled in Medicaid: A quality-of-care study. *Pediatrics, 121*(2), e278–e285. doi:10.1542/peds.2007-0136

Weiss, M. E., Sawin, K. J., Gralton, K., Johnson, N., Klingbeil, C., Lerret, S., . . . Schiffman, R. (2017). Discharge teaching, readiness for discharge, and post-discharge outcomes in parents of hospitalized children. *Journal of Pediatric Nursing, 34*, 58–64. doi:10.1016/j.pedn.2016.12.021

White, R. D. (2011). Designing environments for developmental care. *Clinics in Perinatology, 38*(4), 745–749. doi:10.1016/j.clp.2011.08.012

White-Traut, R., Rankin, K., Fabiyi, C., Liu, L., Cheung, I., & Norr, K. (2017). Maternal characteristics associated with social support in at-risk mothers of premature infants. *Journal of Obstetric, Gynecologic and Neonatal Nursing, 46*(6), 824–833. doi:10.1016/j.jogn.2017.07.008

Whittingham, K., Boyd, R., Sanders, M., & Colditz, P. (2014). Parenting and prematurity: Understanding parent experience and preferences for support. *Journal of Child and Family Studies, 23*(6), 1050–1061. doi:10.1007/s10826-013-9762-x

Williams, T. R., Alam, S., & Gaffney, M. (2015). Progress in identifying infants with hearing loss—United States, 2006-2012. *Morbidity and Mortality Weekly Report, 64*(13), 351–356. Retrieved from https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6413a4.htm?s_cid=mm6413a4_w

Willis, V. (2008). Parenting preemies: A unique program for family support and education after NICU discharge. *Advances in Neonatal Care, 8*(4), 221–230. doi:10.1097/01.ANC.0000333710.83517.19

Wilson, N., Lee, J. J., & Bei, B. (2019). Postpartum fatigue and depression: A systematic review and meta-analysis. *Journal of Affective Disorders, 246*, 224–233. doi:10.1016/j.jad.2018.12.032

Wolke, D., Eryigit-Madzwamuse, S., & Gutbrod, T. (2014). Very preterm/very low birthweight infants' attachment: Infant and maternal characteristics. *Archives of Disease in Childhood—Fetal and Neonatal Edition, 99*(1), F70–F75. doi:10.1136/archdischild-2013-303788

World Health Organization. (2011). *World report on disability 2011*. Retrieved from https://www.who.int/disabilities/world_report/2011/report.pdf

Zabielski, M. T. (1994). Recognition of maternal identity in preterm and fullterm mothers. *Maternal-Child Nursing Journal, 22*(1), 2–36.

Zelkowitz, P., Na, S., Wang, T., Bardin, C., & Papageorgiou, A. (2011). Early maternal anxiety predicts cognitive and behavioural outcomes of VLBW children at 24 months corrected age. *Acta Pædiatrica, 100*, 700–704. doi:10.1111/j.1651-2227.2010.02128.x

Zhang, X., Kurtz, M., Lee, S.-Y., & Liu, H. (2014). Early intervention for preterm infants and their mothers: A systematic review. *Journal of Perinatal and Neonatal Nursing*. Advance online publication. doi:10.1097/jpn.0000000000000065

Unit VII: Neonatal Care in the New Millennium: Challenges and Opportunities

CHAPTER 38

Trends in Neonatal Care Delivery

Carole Kenner and Jana L. Pressler

INTRODUCTION

Today's neonatal care is shaped by the onslaught of Institute of Medicine (IOM) reports in the United States on patient safety, quality, technology, consumer involvement, and the need for an interdisciplinary approach to care. Fiscal constraints coupled with fierce competition have made serious dents in the perinatal regionalization model of care delivery with well-defined levels of care. The Affordable Care Act, which became law in March 2010, and now the proposed repeal, threaten to impact coverage for women and children since it changes funding for Medicaid and women's health services at a time when prematurity rates, especially the late preterm, are on the rise in the United States. In 2010, the IOM released *The Future of Nursing: Leading Change, Advancing Health* report (Committee on the Robert Wood Johnson Foundation Initiative on the Future of Nursing, 2010), which clearly identified nurses as the backbone of healthcare delivery and key players in healthcare reform. As McGrath (2011) noted, changes in healthcare will reconfigure neonatal healthcare. One growing area of change is in follow-up and family-centered care that is in line with the IOM's recommendation for patient-focused care (Greiner & Knebel, 2003). Scientific breakthroughs in genetics and technological advances already have pushed the definition of viability and have brought with them the long-term consequences of comorbidities that can last a lifetime. The demand for evidence to support nursing practice is growing expeditiously.

On the global level, many factors are impacting neonatal care. Most prominent are the Millennium Development Goals (MDGs) and the Sustainable Development Goals (SDGs). This chapter will explore the trends in neonatal care and the nurse's role at the forefront of change.

LEVELS OF CARE

In the early 1990s, the report *Toward Improving the Outcome of Pregnancy II: The 90s and Beyond* (TIOPII; Committee on Perinatal Health, 1993) illustrated the need for levels of care and a regionalization plan for education and practice. The need to have high-risk perinatal care that also provided educational outreach to the community was embraced. The definitions for levels of care were incorporated in the work by the American Academy of Pediatrics (AAP) and the American College of Obstetrics and Gynecology (ACOG) in *Guidelines for Perinatal Care* (AAP & ACOG, 2007). *Toward Improving the Outcome of Pregnancy III* (TIOPIII; March of Dimes [MOD], 2010), like TIOPII, emphasized the need for preconception health through infancy to impact maternal infant outcomes. TIOPIII (MOD, 2010) builds on quality, safety, and performance initiatives for health professionals and healthcare delivery systems. Application of evidence-based care guidelines is a cornerstone of this work. Endorsed by the IOM, the theme of quality of care and safety will continue for many years. Similarly, addressing other key themes is dependent on not only healthcare financing but also differing healthcare needs and healthcare providers' understanding of what is needed and ongoing. The five key TIOPIII (MOD, 2010) themes are:

1. Assuring the uptake of robust perinatal quality improvement and safety initiatives
2. Creating equity and decreasing disparities in perinatal care and outcomes
3. Empowering women and families with information to enable the development of full partnerships between healthcare providers and patients and shared decision making in perinatal care
4. Standardizing the regionalization of perinatal services
5. Strengthening the national vital statistics system (MOD, 2010, p. ix)

The AAP Committee on Fetus and Newborn (COFN; Engel et al., 2004, Stark et al., 2004) acknowledges that as the specialty of neonatal care has become more complex and as smaller and smaller infants have survived, and continue to do so, the three levels of care (i.e., primary, secondary, tertiary) are inadequate in describing the care required. Further, some of the most highly specialized technologies are not needed in every community. Uniformity of care and integration of services are critical to the quality and outcome factors today. Four distinct levels of care are defined in the United States by the *Guidelines for Perinatal Care* (AAP & ACOG, 2017). They are described in Table 38.1.

Newborn Screening

Newborn screening is not a new concept but new conditions are being included. Congenital heart diseases screening has been advocated since 2011. The Centers for Disease Control and Prevention (CDC, 2012) identifies CCHD as comprised of seven distinct defects: hypoplastic left heart syndrome, pulmonary atresia

TABLE 38.1

DEFINITIONS, CAPABILITIES, AND HEALTHCARE PROVIDER TYPES: NEONATAL LEVELS OF CARE

Level of Care	Capabilities	Healthcare Provider Types[a]
Level I: Well newborn nursery	• Provide neonatal resuscitation at every delivery • Evaluate and provide postnatal care to stable term newborn infants • Stabilize and provide care for infants born at 35–37 weeks of gestation who remain physiologically stable • Stabilize newborn infants who are ill and those born before 35 weeks of gestation until transfer to a higher level of care	Pediatricians, family physicians, newborn nurse practitioners, and other nursery advanced practice RNs
Level II: Special care nursery	Level I capabilities plus: Provide care for infants born at 32 weeks of gestation or later and weigh 1,500 g or more who have physiologic immaturity or who are moderately ill with problems that are expected to resolve rapidly and are not anticipated to need subspecialty services on an urgent basis Provide care for infants convalescing after intensive care Provide mechanical ventilation for brief duration (<24 hours) or continuous positive airway pressure or both Stabilize infants born before 32 weeks of gestation and weigh <1,500 g until transfer to a neonatal intensive care facility	Level I healthcare providers plus: Pediatric hospitalists, neonatologists, and neonatal nurse practitioners
Level III: NICU	Level II capabilities plus: Provide comprehensive care for infants born before 32 weeks of gestation and weigh <1,500 g and infants born at all gestational ages and birth weights with critical illness Provide prompt and readily available access to a full range of pediatric medical subspecialists, pediatric surgical specialists, pediatric anesthesiologists, and pediatric ophthalmologists Provide a full range of respiratory support that may include conventional ventilation and/or high-frequency ventilation and inhaled nitric oxide Perform advanced imaging, with interpretation on a urgent basis, including CT, MRI, and echocardiography	Level II healthcare providers plus: Pediatric medical subspecialists,[b] pediatric anesthesiologists,[b] pediatric surgeons, and pediatric ophthalmologists[b]
Level IV: Regional NICU	Level III capabilities plus: Located within an institution with the capability to provide surgical repair of complex congenital or acquired conditions Maintain a full range of pediatric medical subspecialists, pediatric surgical subspecialists, and pediatric anesthesiologists at the site Facilitate transport and provide outreach education	Level III healthcare providers plus: Pediatric surgical subspecialists

[a] Includes all healthcare providers with relevant experience, training, and demonstrated competence.

[b] At the site or at a closely related institution by prearranged consultative agreement.

Source: From American Academy of Pediatrics & American College of Obstetrics and Gynecology. (2017). *Guidelines for perinatal care* (8th ed., pp. 28–30). Elk Grove Village, IL: Author.

(with intact septum), tetralogy of Fallot, total anomalous pulmonary venous return, transposition of the great arteries, tricuspid atresia, and truncus arteriosus. According to the AAP (n.d.), 18/1,000 newborns have a critical congenital heart problem. The rationale for including this type of congenital heart disease screening in the universal newborn screening is that the symptoms representative of these conditions might not be apparent in the neonate prior to hospital discharge (CDC, 2012).

New Jersey enacted mandated screening for Critical Congenital Heart Disease (CCHD) in September, 2011. The screening and follow-up program are led by a neonatal nurse. A reference guide has been developed to help the professional community understand this screening and the needed follow-up (Grazel, 2017). This guide is supported by the New Jersey Department of Health (NJDOH), the American Academy of Pediatrics New Jersey Chapter, and Rutgers University.

Another area of significant concern is high-risk follow-up. As more infants are surviving, the relative lack of consistency of how follow-up is conducted or who is eligible to receive follow-up care serves as a gap in care providers' knowledge. Toward this end, in June 2002, the National Institute of Child Health and Human Development (NICHD), the National Institute of Neurologic Disorders and Stroke (NINDS), and the CDC convened a workshop to examine this gap. They also recognized that differences in data collection methods have led to difficulties with comparing outcomes both within and across centers (NICHD, NINDS, & CDC, 2004). To improve long-term developmental and physical neonatal outcomes, neonatal follow-up care must be clearly

defined with levels corresponding to NICU levels of care. In the next decade, this seminal work will shape the post-NICU experience for neonates and their families. Since 2002, many articles have been published on the lack of uniformity of guidelines for hospital discharge for newborns, the lack of qualified providers available for follow-up and early intervention programs, in spite of referrals to high-risk clinics, a lack of parent preparedness for infant discharge, and the need for more research studies on the post-discharge outcomes of infants who were born with extremely low birth weight, were technology-dependent, or who have had surgery (De Jesus et al., 2012; Dobson & Hunt, 2012; Fink, 2011; Pinto et al., 2012; Smith, Dukhovny, Zupancic, Gates, & Pursley, 2012; Trzaski, Hagadorn, Hussain, Schwenn, & Wittenzellner, 2012). In addition, it has been pointed out that often mothers do not bring their infants back for the first neonatal follow-up appointment postdischarge (Ballantyne, Stevens, Guttmann, Willan, & Rosenbaum, 2012), yet the reasons for this lack of follow-up are unknown, creating another knowledge gap (Ballantyne et al., 2012). An additional area of concern is the missed opportunities for immunizing infants prior to discharge. Navar-Boggan, Halsey, Escobar, Golden, and Klein (2012) found that 27% of infants who were discharged from the NICU at or before 2 months of age had not received any vaccinations. While this study was conducted in 2012, the situation persists today. Immigration status has been implicated as one reason for an increase in under-immunized infants. Many undocumented families fear going to a clinic for this type of care. The Children's National Health System has developed guidelines for caring for this population (Gray & Chapman, 2015).

Family-centered care and the need to include the family in care during the NICU stay, as well as the growing recognition for the need to teach families about developmental care both within and outside the hospital, continue to be at the forefront of neonatal care. Schlittenhart, Smart, Miller, and Severtson (2011) have developed an evidence-based, comprehensive teaching tool for parents of infants discharged from the NICU. This tool exemplifies the trend for more evidence-based guidelines for discharge preparedness. It serves as a critical part of developmental care.

DEVELOPMENTAL CARE

Developmental outcomes have been at the forefront of care for many years but today there is also a movement toward supporting and advocating *individualized family-centered care*. This care coincides with the IOM's (2001) emphasis on patient-focused care as a method to increase quality. Another aspect of this care supports IOM's initiative in interprofessional or interdisciplinary care and that is developmentally supportive care. Individualized family-centered care incorporates knowledge of growth and development; factors that interfere with positive growth such as prematurity, environmental noise, and lighting levels; the interface with physiological responses to stress-inhibited growth factors and increases in cortisol levels; and positioning, to name only a few of the focal topics. Chapter 35, Family: Essential Partner in Care gives more in-depth information on individualized family-centered care.

The NICU environment and its impact on development from a long-term perspective have spawned growth in the use of Recommended Standards for Newborn ICU Design (White, 2012) throughout the world (for more information, see Chapter 32, The Neonatal Intensive Care Unit (NICU) Environment). These recommendations come from an interdisciplinary group of architects, institutional planners, developmental specialists, nurses, physicians, and parents. The use of such standards to renovate or build new NICUs will increase, as will the overall incorporation of individualized, family-centered, developmental care. One example is the publishing of an interdisciplinary book on this subject, *Developmental Care of Newborns and Infants: A guide for health professionals* by Kenner and McGrath (2010). This second edition contains levels of evidence to indicate how developmental interventions are supported by scientific studies. The recognition of neurobehavioral stability and the links to developmental care and long-term outcomes are increasing (Montirosso et al., 2012). Follow-up studies of formerly sick and premature infants are important as they are used to examine developmental outcomes, the need for developmental care from the time of NICU admission, and the potential costs associated with physiological complications and sequelae that might be reduced or avoided with developmental care. Developmental surveillance and screenings are needed if problems are to be detected early (Thomas, Cotton, Pan, & Ratliff-Schaub, 2012).

The National Perinatal Association (NPA) developed psychosocial program standards for NICU parents (Hynan & Hall, 2015). This work underscored the importance of families as a part of neonatal care. It emphasized recognizing that having a baby in a NICU creates the potential for post-traumatic stress in families. These guidelines also suggest that family-centered integrative care is the goal, where the family is integrated into the context of neonatal care. Neonatal Intensive Parenting Unit (NIPU) is a new term that reflects this integration (Hall et al., 2017). An interprofessional team led by Drs. Joy Browne and Carol Jaeger as part of the Gravens Physical Environment of Care for High Risk Newborns is developing competencies that are necessary for everyone who touches a newborn. All of this work includes neuroprotective factors of the neonate and family (Altimier & Phillips, 2013). For more information, see Chapter 32, The Neonatal Intensive Care Unit (NICU) Environment, and the protocol on neuroprotective care (see Protocol II).

Trauma-informed care is another trend that is now reaching the neonatal population. It recognizes, as previously noted, that the NICU is stressful for the neonate and the family. Trauma-informed care helps the health professional to recognize these stresses, minimizes them, and prevents reintroducing trauma (Sanders & Hall, 2018). **Quality and Safety: Its incorporation into the NICU environment is aimed at promoting quality and safety** (Sanders & Hall, 2018). There is a working group examining competencies for neonatal trauma-informed care, led by Mary Coughlin, who wrote the book *Trauma-Informed Care in the NICU* (2016). For more information, please see Chapter 34, Touch a Life, Impact a Lifetime: Trauma-Informed Care in the NICU.

NEONATAL STATISTICS

Neonatal statistics are difficult to follow because of the lack of consistent terminology about the age of the fetus, neonate, and infant. To address that problem, the AAP COFN (Engel et al., 2004, Stark et al., 2004) developed definitions of gestational, postmenstrual, chronological, and corrected ages. These definitions are presented in Table 38.2.

Since 2014, the prematurity rate has risen in the United States. The prematurity rate in the United States was 9.85% in 2016 up from 9.57% in 2014 (Martin, Hamilton, Osterman, Driscoll, & Drake, 2018). A number of factors explain this but the rise in the births of late preterm infants (34–36 weeks of gestation) plays a significant role (Hamilton, Martin, Osterman, Driscoll, & Rossen, 2017). Another contributing factor is the use of assistive reproductive technology (ART; Hwang et al., 2018). The proposed changes

TABLE 38.2

AGE TERMINOLOGY DURING THE PERINATAL PERIOD

Term	Definition	Units of Time
Gestational age	Time between the first day of the last menstrual period and day of delivery	Completed weeks
Chronological age	Time since birth	Days, weeks, months, years
Postmenstrual age	Gestational age + chronological age	Weeks
Corrected age	Chronological age reduced by the number of weeks born before 40 weeks' gestation	Weeks, months

Source: From the Engle, W. A., Blackmon, L. R., Batton, D. G., Bell, E. F., Denson, S. E., Kanto, W. P., Jr., . . . Stark, A. (2004). Age terminology during the perinatal period [Policy statement]. *Pediatrics, 114*(5), 1362–1364. doi:10.1542/peds.2004-1915

in Medicaid and insurance funding in the United States that reduces coverage for women's health services may exacerbate the preterm birth rate.

The neonatal mortality rate in the United States was about 4 deaths per 1,000 live births in 2016 (The World Bank, 2018). According to the Central Intelligence Agency (CIA, 2017), the infant mortality rate in 2017 was still high, at 5.8 deaths per 1,000 live births. These data represent a less than optimal outcome for a resource-rich country such as the United States. The factors that impact these data continue to reflect health disparities, lack of access to care, under- or uninsured women, and the rising preterm birth rates (CDC, n.d.).

The MOD, the World Health Organization (WHO) Partnership for Maternal, Newborn and Child Health, Save the Children, and the WHO, published a report, *Born Too Soon* (Howson, Kinney, & Lawn, 2012), endorsed by more than 40 international organizations, including the Council of International Neonatal Nurses, Inc. (COINN). This report represents a landmark collaboration between governmental and nongovernmental agencies whose sole purpose of working together was to address the Millennium Development Goals—especially #4—to improve outcomes for newborns and infants. The statistics are alarming: 15 million infants worldwide are born preterm; over 1 million children die each year due to prematurity, and prematurity is the leading cause of neonatal deaths and the second leading cause of death of all children under 5 years of age (Howson et al., 2012). The importance of these findings is that healthcare professionals must increase awareness of the serious morbidities associated with prematurity as the MOD and others have done and begin to put resources behind preconception health if one believes that maternal health is inextricably linked to prematurity and other complications. There is also growing recognition that late preterm birth (34–36 6/7 weeks) must be treated as a preterm birth, with late preterm infants receiving appropriate care. The Every Woman Every Child initiative launched by the UN in 2010 calls for action on the part of civil society, nongovernmental, governmental, and professional organizations to develop and implement global strategies to improve health outcomes for women, children, and adolescents (Every Woman Every Child, 2018). This work is linked to the UN Sustainable Development Goals (SDGs). The Every Woman Every Child (2017) progress report calls for the end of preventable deaths. One outcome is to reduce newborn mortality to at least 12 per 1,000 live births in all countries (SDG 3.2; Every Woman Every Child, 2017). Achieving this target is critical to under-five mortality as the largest portion of these deaths are related to the newborn/neonatal period.

MATERNAL/FETAL NEONATAL UNITS

Fetal surgery has been performed for more than three decades. The outcomes of these fetuses/infants have improved as best practices have evolved (Partridge & Flake, 2012; Shue, Harrison, & Hirose, 2012). Until recently, fetuses that remained in utero until a viable birth occurred were cared for in an "everyday" NICU. Now there is recognition of the need for more specialized care for infants who received surgery while in utero. Maternal/fetal/neonatal subunits or additions to NICUs have been developed to provide specialized care. Prototypes of this model are found at the Children's Hospital of Philadelphia (CHOP) and Cincinnati Children's Hospital. These units include perinatal/neonatal/pediatric physician specialists who are familiar with fetal surgery, genetics, pediatric surgery, and the needs of the neonate and family after birth (www.fetalcarecenter.org). These units are growing throughout the United States and address the need for more collaboration between maternal/fetal specialists and neonatal/pediatric specialists. There is now a network for support of these units, Maternal–Fetal Medicine Units (MFMU) Networks (www.nichd.nih.gov/research/supported/mfmu). This growing subspecialty is impacting and expanding the role of neonatal nurse practitioners and nurses. For more information, see Chapter 24, Fetal Therapy.

GENETICS

Genetic breakthroughs as a result of the Human Genome Project (HGP) are influencing health and healthcare. Genomics, the term that refers to the interaction between genetic makeup and the environment, is gradually shaping how health is promoted. The U.S. Surgeon General, along with the work of the National Human Genome Research Institute (NHGRI; www.genome.gov), advocate the use of the Family History Tool that incorporates health history in the traditional sense along with genetic history. Use of this tool coupled with knowledge of newborn screening tests will influence how health professionals plan and implement newborn care. One of the newer areas of emphasis by the NHGRI is severe combined immunodeficiency syndrome (SCID), which appears to be related to several genetic mutations that may be preventable in the future (www.genome.gov/13014325). As another example, if an infant is born to a family with a history of diabetes, the development of healthy eating habits to avoid obesity and other risk factors for diabetes need to begin in the neonatal period. A genomics thrust subsequently changes how care is planned and how it needs to be individualized. It also emphasizes the need for individualized family-centered care. A new trend is the use of genetic knowledge, genomics, and lifestyle to tailor medications and therapies to an individual (U.S. National Library of Medicine, 2018). The trend is referred to as precision health or precision medicine. It is possible in the near future that pain medications, for example, will be ordered according to the genetic makeup of an individual. This trend also calls for a customized treatment plan.

Another aspect of genetics is the controversy over the number of tests that a newborn should have, to prevent long-term complications of neonatal conditions and to improve quality of life. The number of conditions screened varies by state (National Newborn Screening & Global Resource Center, 2018). The questions that arise include: Just because the test can be run and is minimally invasive, should it be done? Who decides? What are the ramifications—is there any danger of insurance discrimination? These ethical questions are at the heart of the debate about newborn screening and the intersection with genetic testing. There are websites and organizations dedicated to providing consumer-friendly information for parents on these topics to help them decide a course of action.

Advances in genetic frontiers will continue to change neonatal care and improve outcomes. One area of growing research is gene therapy in neonates who are diagnosed with Hemophilia B (Lizuka, Sakurai, Tachibana, Chashi, & Mizuguchi, 2017). Stem cell research continues to expand to combat the causes of neonatal morbidity and mortality. This research includes conditions such as bronchopulmonary dysplasia and intraventricular hemorrhage (Chang, Ahn, Sung, & Park, 2017). More research is needed in this area since there are many challenges associated with this therapy (Chang et al., 2017).

GLOBALIZATION

Recommendations for NICU standards and professional programs such as Neonatal Resuscitation, S.T.A.B.L.E. (Sugar & Safe Care, Temperature, Airway, Blood Pressure, Lab Work, and Emotional Support [www.stableprogram.org]), and Helping Babies Breathe supported by the AAP (https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/helping-babies-survive/Pages/Helping-Babies-Breathe.aspx) are being used globally. Neonatal care issues are international. The era of globalization is changing the way care practices and outcomes are viewed. Protocols for care are developed so that they can be adapted for cultural sensitivity, technology availability, and geographic needs. The push toward evidence-based practice and the use of Cochrane reviews, the Joanna Briggs Institute Collaborative Systematic Reviews, and Vermont Oxford materials all are bringing neonatal care to a level that is supported by scientific findings rather than primarily by tradition. This movement is global and is being influenced by hospitals seeking Magnet status; it espouses evidence-based practice guidelines to ensure quality care and more positive outcomes. As this influence continues, there will be shifts in how care is implemented. The COINN (www.coinnurses.org) is partnering with other organizations such as the European Foundation for the Care of Newborn Infants (www.efcni.org), the White Ribbon Alliance for Safe Motherhood (www.whiteribbonalliance.org), and many others worldwide to address policy, care, education, and research initiatives that touch the lives of mothers, fathers, newborns, and their siblings. These collaborations with the use of social media tools, listservs, and blogs will only increase in the next few years. Evidence-based guidelines for care are being adapted for use worldwide. A major challenge for this work, from a nursing perspective, is that there is no consistent definition of a nurse or a neonatal nurse. In some countries there are regulations and consistent education but in others neither of these exist for any level/type of nurse. COINN is working on the development of competencies to define the neonatal nurse. One example of a growing global area of special concern is palliative care for infants.

PALLIATIVE AND END-OF-LIFE CARE

There is an increasing awareness of the need for effective pain management. The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) has declared pain as the fifth vital sign across the life span. For neonates, pain management is complicated by the patient's nonverbal status and the need to rely on physiological parameters to measure pain and pain management responses. There is a need for more evidence to support pain management as seen in Chapter 23, Pain in the Newborn and Infant. Neonatal palliative care recognition is growing. As part of the National Perinatal Association's (NPA) project on psychosocial program standards for NICU parents, bereavement and palliative care recommendations were included (Hynan & Hall, 2015). Inclusion of this type of care is part of the Quality and Safety movement in neonatal care (Purdy et al., 2017).

Whether anyone wants to acknowledge it or not, some children are born dying. There are infants who cannot be saved despite the availability of sophisticated technology, and others who have life-threatening illnesses and who can survive. Those in the latter group, like all patients, deserve comfort or palliative care. (See Chapter 36, Palliative and End-of-Life Care, for more information.)

Population Health

The National Institutes of Health (NIH) has expanded funding to support development of the Centers for Population Health and Health Disparities. These centers focus on developing strategies to address disparities to include the social determinants of health—social, behavioral, genetic, environmental, and biological. There are many practical applications of population health in neonatal/family care. Population health refers to actions or factors, such as maternal factors, that impact the health outcomes of the infant. Preconception health, factors that relate to prematurity, and neonatal illness are examples of areas that fit within population health. Brindle, Flageole, and Wales (2012) examined maternal factors that might affect the health outcomes of infants with gastroschisis. This study was conducted in Canada and found that younger women who used drugs during pregnancy in rural or very isolated regions of Canada were giving birth to infants with gastroschisis (Brindle et al., 2012). This study is an example of population health and the linkages with social determinants and with specific neonatal conditions for neonates and their families.

The Robert Wood Johnson Foundation awarded grants to support the infusion of population health principles into undergraduate nursing curricula. Healthcare organizations have set up population health departments to address the most costly conditions experienced by patients and families. These usually include asthma, cardiovascular disease, and diabetes. The population health movement has yet to address neonatal health comparable to adult health even though there are some examples as previously noted.

PARENT VOICES

Jennifer Degl

NICU discharge day was something we had dreamed and wished for, yet is was one of the scariest days (aside from my daughter's premature birth) in our journey. For months, we looked forward to the day that we could bring home our baby to join our family. Once we arrived at home, the fear set in. How could we care for this precious baby with complex medical needs? How would we know if she stopped breathing while she slept? How would we know if she was choking while she ate or if she had an episode of reflux while napping? How would we be able to keep her safe and alive? These are all very valid questions since the nurses are the baby's primary caregivers while in the NICU. The fear is real but what is also real is that the hospital staff would not send the baby home if they felt that the baby would not be safe. Most parents begin to isolate themselves and their babies once they are discharged from the NICU because it's very important to keep the germs away. This can cause parents to feel very lonely. Parents should seek online support groups for NICU or premature babies because the members understand and can offer advice on how to manage after discharge. Parents should also be open to counseling. Most parents do not have time to process what has happened while their baby is still in the hospital and often have more time to reflect after discharge. This can trigger a plethora of emotional responses and there is nothing wrong with asking for professional support to help the healing process.

SUMMARY

This chapter has briefly highlighted some of the recent trends in neonatal care. With all the new breakthroughs in care, it is hard to imagine what the next decade will bring.

ONLINE RESOURCES

American Academy of Pediatrics. *Helping babies breathe*. Retrieved from https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/helping-babies-survive/Pages/Helping-Babies-Breathe.aspx

Caring Essentials. *Trauma-informed neuroprotective care for hospitalized infants, families and staff*. Retrieved from https://www.caringessentials.net

Council of International Neonatal Nurses, Inc. Retrieved from https://www.coinnurses.org

KidsHealth. (n.d.). *Genetic testing*. Retrieved from http://kidshealth.org/parent/system/medical/genetics.html

Maternal-Fetal Medicine Units (MFMU) Networks. Retrieved from https://www.nichd.nih.gov/research/supported/mfmu

The S.T.A.B.L.E. Program. Retrieved from https://stableprogram.org

REFERENCES

Altimier, L., & Phillips, R. M. (2013). The neonatal integrative developmental care model: Seven neuroprotective core measures for family-centered developmental care. *Newborn & Infant Nursing Reviews, 13*(1), 9–22. doi:10.1053/j.nainr.2012.12.002

American Academy of Pediatrics. (n.d.). *Program to Enhance the Health & Development of Infants and Children (PEHDIC)*. Retrieved from https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/PEHDIC/Pages/Newborn-Screening-for-CCHD.aspx

American Academy of Pediatrics & American College of Obstetrics and Gynecology. (2007). *Guidelines for perinatal care* (6th ed.). Elk Grove Village, IL: Author.

American Academy of Pediatrics & American College of Obstetrics and Gynecology. (2017). *Guidelines for perinatal care* (8th ed., pp. 28–30). Elk Grove Village, IL: Author.

Ballantyne, M., Stevens, B., Guttmann, A., Willan, A. R., & Rosenbaum, P. (2012). Transition to neonatal follow-up programs: Is attendance a problem? [Research Support, Non-U.S. Gov't]. *Journal of Perinatal and Neonatal Nursing, 26*(1), 90–98. doi:10.1097/JPN.0b013e31823f900b

Barfield, W. D., Papile, L.-A., Baley, J. E., Benitz, W., Cummings, J., Carlo, W. A., . . . Watterberg, K. L. (2012). AAP policy statement: Levels of neonatal care. *Pediatrics, 130*(3), 587–597. doi:10.1542/peds.2012-1999

Brindle, M. E., Flageole, H., & Wales, P. W. (2012). Influence of maternal factors on health outcomes in gastroschisis: A Canadian population-based study. *Neonataology, 102*(1), 45–52. doi:10.1159/000336564

Centers for Disease Control and Prevention. (n.d.). Reproductive health: Infant mortality. Retrieved from https://www.cdc.gov/reproductivehealth/maternalinfanthealth/infantmortality.htm

Centers for Disease Control and Prevention. (2012). Screening for critical congenital heart defects. *Pediatric Genetics*. Retrieved from https://www.cdc.gov/ncbddd/heartdefects/cchd-facts.html

Central Intelligence Agency. (2017). *The world factbook: Country comparison: Infant mortality rate*. Retrieved from https://www.cia.gov/library/publications/the-world-factbook/rankorder/2091rank.html

Chang, Y. S., Ahn, S. Y., Sung, S., & Park, W. S. (2017). Stem cell therapy for neonatal disorders: Prospects and challenges. *Yonsei Medical Journal, 58*(2), 266–271. doi:10.3349/ymj.2017.58.2.266

Committee on Perinatal Health. (1993). *Toward improving the outcome of pregnancy: The 90s and beyond*. White Plains, NY: March of Dimes Birth Defects Foundation.

Committee on the Robert Wood Johnson Foundation Initiative on the Future of Nursing. (2010). *The future of nursing: Leading change, advancing health*. Washington, DC: National Academies Press. Retrieved from https://www.nap.edu/read/12956/chapter/1

Coughlin, M. (2016). *Trauma-informed care in the NICU: Evidence-based practice guidelines for neonatal clinicians* (1st ed.). New York, NY: Springer Publishing Company.

De Jesus, L. C., Pappas, A., Shankaran, S., Kendrick, D., Das, A., Higgins, R. D., & Human Development Neonatal Research Network. (2012). Risk factors for post-neonatal intensive care unit discharge mortality among extremely low birth weight infants. *Journal of Pediatrics, 161(1)*, 70–74. doi:10.1016/j.jpeds.2011.12.038

Dobson, N. R., & Hunt, C. E. (2012). Interinstitutional variability in home care interventions after neonatal intensive care unit discharge [Comment Editorial]. *The Journal of Pediatrics, 160*(2), 187–188. doi:10.1016/j.jpeds.2011.09.033

Engle, W. A., Blackmon, L. R., Batton, D. G., Bell, E. F., Denson, S. E., Kanto, W. P., Jr., . . . Stark, A. (2004). Age terminology during the perinatal period [Policy statement]. *Pediatrics, 114*(5), 1362–1364. doi:10.1542/peds.2004-1915

Every Woman Every Child. (2017). *2017 Progress report on the Every Woman Every Child global strategy for women's, children's and adolescents' health*. Retrieved from http://gsprogressreport.everywomaneverychild.org

Every Woman Every Child. (2018). Every Woman Every Child. Retrieved from https://www.everywomaneverychild.org/

Fink, A. M. (2011). Early hospital discharge in maternal and newborn care [Historical Article]. *Journal of Obstetric, Gynecologic, and Neonatal Nursing, 40*(2), 149–156. doi:10.1111/j.1552-6909.2011.01225.x

Gray, M., & Chapman, J. (2015). *Guidelines for pediatric immigrant health: Future of pediatrics 2015*. Washington, DC: Children's National Health System.

Grazel, R. (2017). *Critical congenital heart defects screening: New Jersey Reference Guide*. Retrieved from https://nj.gov/health/fhs/nbs/documents/cchd_screening_guide.pdf

Greiner, A. C, & Knebel, E. (Ed.). (2003). *Health professions education: A bridge to quality*. Washington, DC: National Academies Press.

Hall, S. L., Hynan, M. T., Phillips, R., Lassen, S., Craig, J. W., Gover, E., . . . Cohen, H. (2017). The neonatal intensive parenting unit: An introduction. *Journal of Perinatology, 37*(12), 1259–1264. doi:10.1038/jp.2017.108

Hamilton, B. E., Martin, J. A., Osterman, M. J. K., Driscoll, A. K., & Rossen, L. M. (2017). *Births: Provisional data for 2016. NVSS-Vital Statistics Rapid Release* (Report No. 002). Hyattsville, ND: U.S. Department of Health and Human Services—Centers for Disease Control and Prevention. Retrieved from https://www.cdc.gov/nchs/data/vsrr/report002.pdf

Howson, C. P., Kinney, M. V., & Lawn, J. E. (Eds.). (2012). *Born too soon: The global action report on preterm birth*. Geneva, Switzerland: World Health Organization. Retrieved from http://www.who.int/pmnch/media/news/2012/201204_borntoosoon-report.pdf

Hwang, S. S., Dukhovny, D., Gopal, D., Cabral, H., Missmer, S., Diop, H., . . . Stern, J. E. (2018). Health of infants after ART treated, subfertile, and fertile deliveries. *Pediatrics, 142*(2), e20174069. doi:10.1542/peds.2017-4069. Retrieved from http://pediatrics.aappublications.org/content/pediatrics/early/2018/06/29/peds.2017-4069.full.pdf

Hynan, M. T., & Hall, S. L. (2015). Psychosocial program standards for NICU parents. *Journal of Perinatology, 35*(Suppl. 1), S1–S4. doi:10.1038/jp.2015.141

Institute of Medicine. (2001). *Crossing the quality chasm: The IOM health care quality initiative*. Washington, DC: National Academies Press.

Kenner, C., & McGrath, J. M. (2010). *Developmental care of newborns and infants: A guide for health professionals* (2nd ed.). Glenview, IL: National Association of Neonatal Nurses.

Lizuka, S., Sakurai, F., Tachibana, M., Chashi, K., & Mizuguchi, H. (2017). Neonatal gene therapy for hemophilia B by a novel adenovirus vector showing reduced leaky expression of viral genes. *Molecular Therapy Methods & Clinical Development, 6*, 183–193. doi:10.1016/j.omtm.2017.07.001

March of Dimes. (2010). *Toward improving the outcome of pregnancy III (TIOPIII): Enhancing perinatal health through quality, safety and performance initiatives*. White Plains, NY: Author.

Martin, J. A., Hamilton, B. E., Osterman, M. J. K., Driscoll, A. K., & Drake, P. (2018). *Births: Final data for 2016* [National Vital Statistics Reports, Vol. 67, No. 1]. Hyattsville, MD: U.S. Department of Health & Human Services—Centers for Disease Control and Prevention. Retrieved from https://www.cdc.gov/nchs/data/nvsr/nvsr67/nvsr67_01.pdf

McGrath, J. M. (2011). Expert opinion-neonatal healthcare: What does the future hold? *Journal of Perinatal and Neonatal Nursing, 25*(3), 219–221. doi:10.1097/JPN.0b013e3182187197

Montirosso, R., Del Prete, A., Bellu, R., Tronick, E., Borgatti, R., & Neonatal Adequate Care for Quality of Life Study Group. (2012). Level of NICU quality of developmental care and neurobehavioral performance in very preterm infants [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. *Pediatrics, 129*(5), e1129–e1137. doi:10.1542/peds.2011-0813

National Institute of Child Health and Human Development, National Institute of Neurologic Disorders and Stroke, & Centers for Disease Control and Prevention. (2004). Follow-up care of high-risk infants. *Pediatrics, 114*(Suppl. 5), 1377–1397. doi:10.1542/peds.2004-0866

National Newborn Screening & Global Resource Center. (2018). *Families: Newborn screening*. Retrieved from http://genes-r-us.uthscsa.edu/resources/consumer/statemap.htm

Navar-Boggan, A. M., Halsey, N. A., Escobar, G. J., Golden, W. C., & Klein, N. P. (2012, May). Under-immunization at discharge from the neonatal intensive care unit [Research Support, Non-U.S. Gov't]. *Journal of Perinatology, 32*(5), 363–367. doi:10.1038/jp.2011.111

Partridge, E. A., & Flake, A. W. (2012). Maternal–fetal surgery for structural malformations. *Best Practice & Research. Clinical Obstetrics & Gynaecology, 26*(5), 669–682. doi:10.1016/j.bpobgyn.2012.03.003

Pinto, N. M., Lasa, J., Dominguez, T. E., Wernovsky, G., Tabbutt, S., & Cohen, M. S. (2012). Regionalization in neonatal congenital heart surgery: The impact of distance on outcome after discharge. *Pediatric Cardiology, 33*(2), 229–238. doi:10.1007/s00246-011-0116-4

Purdy, I. B., Melwak, M. A., Smith, J. R., Kenner, C., Chuffo-Siewert, R., Ryan, D. J., . . . Samra, H. A. (2017). Neonatal nurses NICU quality improvement. *Advances in Neonatal Care, 17*(1), 33–44. doi:10.1097/ANC.0000000000000352

Sanders, M. R., & Hall, S. L. (2018). Trauma-informed care in the newborn intensive care unit: Promoting safety, security and connected ness. *Journal of Perinatology, 38*(1), 3–10. doi:10.1038/jp.2017.124

Schlittenhart, J. M., Smart, D., Miller, K., & Severtson, B. (2011). Preparing parents for NICU discharge: An evidence-based teaching tool. *Nursing for Women's Health, 15*(6), 485–494. doi:10.1111/j.1751-486X.2011.01676.x

Shue, E. H., Harrison, M., & Hirose, S. (2012). Maternal–fetal surgery: History and general considerations. *Clinics in Perinatology, 39*(2), 269–278. doi:10.1016/j.clp.2012.04.010

Smith, V. C., Dukhovny, D., Zupancic, J. A., Gates, H. B., & Pursley, D. M. (2012). Neonatal intensive care unit discharge preparedness: Primary care implications. *Clinical Pediatrics, 51*(5), 454–461. doi:10.1177/0009922811433036

Stark, A., Blackmon, L. R., Batton, D. G., Bell, E. F., Denson, S. E., Engle, W. A., . . . Martin, G. I. (2004). Levels of neonatal care [Policy statement]. *Pediatrics, 114*(5), 1341–1347. doi:10.1542/peds.2004-1697

Thomas, S. A., Cotton, W., Pan, X., & Ratliff-Schaub, K. (2012). Comparison of systematic developmental surveillance with standardized developmental screening in primary care. *Clinical Pediatrics, 51*(2), 154–159. doi:10.1177/0009922811420711

Trzaski, J. M., Hagadorn, J. I., Hussain, N., Schwenn, J., & Wittenzellner, C. (2012). Predictors of successful discontinuation of supplemental oxygen in very low-birth-weight infants with bronchopulmonary dysplasia approaching neonatal intensive care unit discharge. *American Journal of Perinatology, 29*(2), 79–86. doi:10.1055/s-0031-1295646

U.S. National Library of Medicine. (2018). Genetics Home Reference: What is precision medicine? Retrieved from https://ghr.nlm.nih.gov/primer/precisionmedicine/definition

White, R. (2012). *Recommended standards for newborn ICU design: Report of the Eighth Consensus Conference on Newborn ICU Design*. Retrieved from http://www.nd.edu/~nicudes

The World Bank. (2018). *Mortality rate, neonatal (per 1,000 live births)*. Retrieved from https://data.worldbank.org/indicator/SH.DYN.NMRT

CHAPTER 39

Neonatal Care Using Informatics

Susan K. Newbold

INTRODUCTION

Hospitals have successfully used information technology (IT) in the past decades to support administrative, financial, and some clinical functions. Recent governmental mandates to reform healthcare have awakened the interest of many hospitals and provider practices to the value of using IT to support patient care. Effective use of IT in neonatal intensive care units (NICUs) or any intensive care unit (ICU) may greatly improve patient care and patient outcomes, reduce clinician workload, and decrease costs. Adoption of computerized technologies holds great promise as computer systems improve each year. Full functionality requires the integration of healthcare systems through adherence to emerging industry standards for computer-to-computer communication, healthcare data vocabularies, and quality management. This chapter focuses on the current status and near-future advances of NICU IT and provides guidance for evaluating and choosing information systems (IS) for the NICU.

BACKGROUND INFORMATION

The evolution of informatics began in the late 1950s as healthcare and computer technology began to blend. According to Collen (1995), the term *medical informatics* first appeared in 1974 and became pervasive in the 1980s with the introduction of microcomputers and networked computers. Some suggest that informatics was created as a new field with the first computerization of a cardiac catheterization laboratory by Dr. Homer Warner, Sr. Informatics expanded quickly as external technological innovations diffused throughout the heathcare environment. Informatics pioneers were first classified as a subgroup of bioengineering. Many new names for the field appeared: medical computer science, medical information processing, and medical computer technology. Over time, healthcare professionals began substituting the term *medical* with *health* because informatics is a broad term that pertains to many healthcare disciplines, not just medicine. By the 1980s, the terms *clinical*, *health*, and *nursing* informatics had surfaced. Saba and McCormick (2015) assert that the field of informatics exploded in nursing in the 1980s. The nursing profession needed to update its practice standards and determine the data standards, vocabularies, and classification schemes that could be used for electronic patient record systems.

Nursing informatics (NI) has evolved rapidly from the predominantly physician-populated field of medical informatics. Nurses Graves and Corcoran, authors of "The Study of Nursing Informatics," defined NI as "a combination of computer science, information science, and nursing science designed to assist with the management and processing of data, information, and knowledge to support the practice of nursing and the delivery of nursing care" (Graves & Corcoran, 1989, p. 227).

Graves and Corcoran's classic definition considered functional components (i.e., management and processing), combined with conceptual components (i.e., data, information, and knowledge), and then recognized the *process* whereby the functional components operate on the conceptual components. In short, Graves and Corcoran believe that NI should be more concerned with how the data is structured and organized than with the content of the data.

In this early stage of development, informatics continues to morph and to grow rapidly. The two strongest influences on the informatics field are evolving healthcare and advances in technology. Informatics attempts to merge these two dynamic influences to better the delivery of healthcare.

A workgroup sponsored by the American Nurses Association (2015) utilized the Graves and Corcoran concept to create this definition of NI, well accepted in the United States:

> Nursing informatics (NI) is a specialty that integrates nursing science with multiple information and analytical sciences to identify, define, manage, and communicate data, information, knowledge, and wisdom in nursing practice. NI supports nurses, consumers, patients, users, the interprofessional healthcare team, and other stakeholders in their decision-making in all roles and settings to achieve desired outcomes. This support is accomplished through the use of information structures, information processes, and IT. (p. 1)

Landmark legislation in 2010 advanced electronic health records (EHRs) extensively in the United States. The Health Information Technology for Economic and Clinical Health (HITECH) Act, passed in 2009, offered financial incentives for meeting the first of a series of tests of the *meaningful use* of healthcare IT. It was expected that there would be three stages to be achieved to realize maximum incentive payments to eligible providers and to avoid financial penalty. As of this writing, the requirements for Stage II have been adopted. In Stage II, the goal is to increase health information exchange between providers and promote

patient engagement by giving patients secure online access to their health information.

The Healthcare Information Management Systems Society (HIMSS) Analytics (2018) offers an eight-stage U.S. EMR Adoption Model[SM] that reveals how facilities have progressed with the implementation of EHRs. As of the end of 2017, 83.3% of the 5,487 facilities reporting indicated they have IS that support computerized physician order entry (CPOE) with clinical decision support, nursing and allied health documentation, and basic business continuity (HIMSS Analytics, 2018). Only 6.4% of facilities have reached the highest level with a complete electronic medical record; external health information exchange, data analytics, governance, disaster recovery, privacy, and security.

SPECIAL CONSIDERATIONS FOR THE EHR IN SUPPORTING PEDIATRIC AND NEONATAL PATIENT CARE

Lowry et al. (2012) published "A Human Factors Guide to Enhance EHR Usability of Critical User Interactions When Supporting Pediatric Patient Care" highlight clinically important special considerations for pediatric patients that are often not understood by those selecting IS for the adult population.

- Weight-based dosing in the NICU is far more complex and difficult to standardize.
- Sophisticated rounding strategies and accurate weight measurements are used to avoid over- or underdosing, especially for infants who weigh less than 1,000 g.
- Patients can share the same birth date with multiple siblings, so identification can be an issue.
- Alerts can be challenging due to the need for both age- and weight-based alerts. Age-based dosing considerations in neonates must also consider gestational age, elapsed days since birth, and *adjusted chronologic age* for growing very low birth weight babies.

TYPES OF INFORMATION SYSTEMS

According to McGonigle and Mastrian (2018), the term *information system* refers to "the manual and/or automated components of [sic] system of users or people, recorded data, and actions used to process the data into information for a user, group of users, or an organization" (p. 568). Others argue that IS also include those manual data management systems that still exist in parallel today. More specifically, clinical IS are IS that provide access to and methods for recording and managing clinical data. Examples include paper and electronic flow sheets, daily notes, physician orders, and pharmaceutical systems.

FLOW SHEET REPLACEMENT AND CLINICAL MONITORING

Critical care bedside clinicians are *hands-on* providers. The care environment is complex and filled with many simultaneous processes that inform medical decision making. ICUs are often crowded with both people and devices. Care providers are often summoned from one task to a more urgent one in seconds, making computer use/access/log off difficult or impossible with existing systems. Clinical data acquisition and integration at most ICU bedsides still depend on pen-and-paper flow sheet methods and workarounds. This practice is very time consuming and creates an *information overload* of poorly organized, often illegible data that can lead to oversights and potentially avoidable errors (Palma, Brown, Lehmann, & Longhurst, 2012; Salanova, Llorens, & Cifre, 2012).

Real-time integration of machine and ancillary data into a user-defined presentation format to support bedside patient care is an unmet dream of most intensive care doctors and practitioners. Past attempts to computerize aspects of ICU bedside physiologic data management have led to sophisticated, freestanding commercial bedside physiologic monitoring and treatment systems (monitors, ventilators, pumps, and flowmeters). Each machine relates to a subset of the patient's overall problems (cardiac, respiratory, brain, etc.). Unfortunately, these existing bedside machines have no formal open communication standards with today's computers, although we are moving toward adopting standards.

A challenge for NICU computerization is acquiring and integrating important off-site ancillary data such as that from laboratory, pharmacy, and radiology departments. Computer tools to obtain, analyze, and present patient data trends and information important for clinical caregivers in complicated ICU situations are emerging and are becoming commercially available, usually as *templates* that require local programming.

As flow sheet replacement systems evolve, more complete solutions are being developed to reduce the drawbacks that have prevented the adoption of many of the early electronic flow sheet systems. The more complete solutions enable real-time temporal integration and storage of clinical patient information derived from many different clinical data sources. They have effective interfaces to analyze and display this data both for immediate patient care and for clinical research and quality assurance initiatives. Some of these new systems have touchscreen interfaces available that provide a single point of contact for viewing patient data that is stored in EHR systems, laboratory systems, and pharmacy systems along with data collected from the output of attached bedside machines. This type of automated integration greatly reduces the amount of bedside clinical patient data that must be reentered by the bedside nurse. Time-sensitive graphical displays provide a convenient mechanism for caregivers to review current and historical data about the patient so clinicians can quickly grasp a more complete picture of a critical care patient's status. With real-time integrated systems, many critical transients (e.g., apnea and bradycardia episodes) or trends (e.g., loss of heart rate variability) are harder to overlook in situations where multiple simultaneous events compete for a caregiver's time, such as crisis situations during transport or in the ICU. The most complete of these automated flow sheet systems improve upon current practices by means of the following:

- Integrating important data from the EHR, laboratory, pharmacy, and bedside devices, then displaying the temporal information clearly and compactly at the patient bedside or point of care
- Capturing and integrating patient parameters (vital signs, labs, etc.) into a daily note system
- Enabling remote access to integrated patient data, just as if the clinician were at the point of care
- Interfacing patient data collected during transport with the patient electronic record
- Providing deidentified or scrubbed patient information securely to a data warehouse for supporting a broad range of quality assurance, medical, pharmaceutical, and bioinformatics research activities
- Utilizing the automatically captured, integrated data to suggest diagnostics, suggest protocol adherence, and provide smart alert notifications.

Current paper-based flow sheet standards have been seemingly adequate throughout history. It is evident, however, that a properly

designed automated flow sheet system could decrease time collecting, communicating, and analyzing patient data. This saved time can then allow clinicians to focus more on treatment and patient care.

INTERDISCIPLINARY NOTES: DAILY DOCUMENTING CHALLENGES

Every day, in every ICU, many different notes must be generated that outline the care being provided for the patient by the nurse, the doctor, the respiratory therapist, and others on the care team (pharmacists, social workers, physical therapists, etc.). Generating these notes, from the initial history and physical (H&P), to the daily progress note, to the final discharge note, has often been problematic and is very time consuming.

The information contained in many of these notes is used for both communicating and documenting daily care and eventually for billing. Over the years, attempts to generate a *readable* note have taken on several forms. Traditionally, a clinician would record a few key words when moving from patient to patient or use a preprinted card with check boxes to record appropriate information. Later, in a more private, less chaotic space, the clinician may try to recall everything about the encounter and create a narrative note. The clinician might type the note, but this data entry method has slowed, and often disgruntled, clinicians. More often, the clinician would dictate the encounter narrative to a dictation service. Some number of hours or days later, a complete note would appear for the clinician to sign and place in the chart, as a prerequisite for reimbursement. The dictation is expensive for the hospital. The delay in returning the dictation to the care venue, plus the delay in signing, compounds ongoing operational problems of timely coordination of daily communication between different caregivers, especially in a cross-disciplinary, teamwork-based NICU.

Several companies have developed voice recognition systems to overcome the delay-related issues. In disciplines with *limited* vocabulary and quiet work environments (e.g., radiology), voice recognition systems have achieved some popularity. If voice recognition systems can be made to work well, the daily note is theoretically available as soon as the clinician finishes speaking; edits can be made immediately. The usual drawback of such systems is that the *vocabulary* to be recognized must be greatly restricted in order for the system to work well. In addition, each clinician using the system must *train* the system to recognize his or her personal speech patterns. Extraneous noise can greatly influence the accuracy of the word recognition, so the dictation must be done in a relatively quiet environment, which is difficult to attain in the daily life of most NICUs. To achieve this, the clinician must, once again, be removed from the point of care to record the encounter. This can lead to errors and often requires first written, then verbal narration of facts in hopes of precisely recording the encounter. Increasing point-of-care clinician absence can lead to team communication gaps, errors, and redundant *documentation*, potentially causing decreased accuracy and wasting precious time duplicating facts. This dysfunctional workflow situation leads to increased caregiver frustration, and therefore decreased product usage. When used in an optimal setting, however, voice recognition systems often excel.

Daily note systems based on templates are gaining popularity. A template is a document in either paper or electronic format that contains commonly used clinical data elements in a predefined format. The idea behind these templates is that the format of the template (e.g., daily note) is fairly static for a given patient type (neonate, cardiac, transplant, etc.). One of the more tedious tasks when using this writing system is gathering parameters (such as blood pressure, O_2Sat, and heart rate from the flow sheet) and retyping them. Another downfall is that the users could begin to rely only on those predefined elements within the template, thereby potentially missing unusual findings or situations. Templates that utilize a note system configured to accept bedside data from an automated data acquisition system can greatly reduce the time needed to generate daily notes and can often increase completeness and comprehensibility of the daily note.

COMPUTERIZED PROVIDER ORDER ENTRY/MANAGEMENT

Meaningful use and the HITECH legislation have significantly advanced CPOE. The promise of these systems includes reduction in errors through improved legibility, immediate cross-checking for prescription interactions, other error alerts, and more immediate fulfillment of orders. Currently 83.3% of 5,487 hospitals are using CPOE, which is a significant jump from 2012, when only about 13.3% of hospitals were using CPOE (HIMSS Analytics, 2018). Poor training and system usability seem to be the root causes of problems with the early use of CPOE (Kuperman & Gibson, 2003). Although some hospitals have experienced failures implementing CPOE systems, there are also many hospitals with successful implementations. Among these success stories, studies have indicated benefits such as a reduction in medical errors, improved quality of patient care, and a positive effect on costs of healthcare are directly related to CPOE systems (Chapman, Lehmann, Donohue, & Aucott, 2012; Mekhjian et al., 2002; Saathoff, 2005). For neonates, the CPOE systems were rudimentary and often required extreme caregiver time and attention to dealing with difficult computer system navigation and workarounds, including defining pharmacy compounding, details that are usually unfamiliar to bedside clinicians. CPOE implementations themselves are often locally adapted from adult systems, leaving gaps and internal coding (e.g., rounding rules for 500 g infants) that may be inconsistent with optimizing clinical care in the NICU.

Chapman et al. (2012) studied the implementation of CPOE in an NICU. The researchers conducted a one process-focused hospital study to determine if CPOE impaired or enhanced workflow in the NICU. By comparing the timing of administration of antibiotics before and after CPOE implementation, they concluded that CPOE in the NICU did not significantly improve antibiotic administration times, but the time to pharmacy verification was improved. This suggested further work was needed to investigate admission workflow, which they deemed to be a complex process.

Unintended consequences of EHR use including CPOE have been studied among physicians but few studies focus on nurses in the neonatal intensive care. Dudding, Gephart, and Carrington (2018) examined the unintended consequences of nurses' use of EHRs and included neonatal nurses in the sample. They defined unintended consequences as "unforeseen events, change in workflow, or an unanticipated result of implantation and use of electronic health records" (p. 167). Interruptions, a heavier workload due to the EHR, changes to the workflow, and altered communication patterns were the most frequent unintended consequences cited.

PHARMACY

Pharmacy-related electronic IS have been introduced in recent years that have reduced medication errors, thereby preventing harm to our tiniest patients. Many ICUs have adopted electronic dispensing systems to help ensure that the ordered medicine is given to the correct patient. Barcode medication administration is in the

process of being widely adopted and the level of adoption stands at 33.8% in 2018, up from 11.5% in 2012 (HIMSS Analytics, 2018). With such a system, barcode labels on the medication (including breast milk) are scanned along with a barcode identification band on the patient, ensuring that the appropriate medication is given to the appropriate patient in the right dose at the right time and through the correct route. If all is correct, the nurse or other healthcare professional gives the medication and records the event in the electronic record. These systems require barcodes to be assigned to a patient and to each prescription filled by the pharmacy. In order for these systems to be most effective, a medication history must be made available to the pharmacy plus someone must be available to enter the historical data, both at admission and after every *transition of care* (e.g., a trip to the operating room and back).

OTHER SYSTEMS

In addition to the systems outlined, many other computerized systems exist within hospital settings that provide data regarding a patient's condition. Imaging systems to store and display x-ray, CT scan, and MRI results are widely available. Laboratory systems that can send information to the EHR or store the results locally are being used by modern hospitals.

More and more NICUs are utilizing telehealth technologies to allow virtual visitations of the infant by family members. A study of the impact of web cameras advises that disruption of the nurse workflow has the potential to decrease the quality of care for infants. Researchers suggest that, to mitigate for the disruptions, training sessions should be held with nursing staff prior to system implementation (Joski, Chyou, Tirmizi, & Gross, 2016).

An underlying layer of complexity with all of the aforementioned systems is the hardware that is used to display the data. For example, most hospitals' IS are *hardwired*, requiring a clinician to view and document patient data at a stationary computer. A rapidly emerging option is to make most interfaces *wireless*, allowing mobile access to patient information. Wireless solutions include laptop personal computers, tablets, personal computers, and smartphones.

The problem with having so many different IS is that ensuring accurate communication between systems is difficult. Such difficulties as terminology differences among systems, multiple log ins, variable security protocols, and reducing data redundancy all point to a more complex integration problem. Lack of computer communication standards to express the broad spectrum of neonatal and perinatal diseases and transitional difficulties compounds the problem set.

Interoperability (HIMSS, 2018) "describes the extent to which systems and devices can exchange data, and interpret that shared data. For two systems to be interoperable, they must be able to exchange data and subsequently present that data such that it can be understood by a user." The Centers for Medicare and Medicaid Services (CMS) has renamed the meaningful use EHR Incentive Programs as Promoting Interoperability (PI) Programs (CMS, 2019).

INTEGRATING COMPUTERS

Integration issues can be likened to language barriers. Suppose the organization's flow sheet system was in Spanish, the daily notes system in Russian, and the pharmacy system in Chinese. Obviously, communication would be difficult unless one spoke all three languages or had interpreters. In informatics, the *interpreter* that would make the aforementioned systems communicate is called an *interface*. Currently, interfaces are necessary because independent systems (flow sheet, daily notes, pharmacy, laboratory, etc.) within a hospital need to communicate patient information with each other and the end users. Although interfaces are currently necessary as an interim solution, they are not perfect. In ICUs, optimal clinical care depends on clear integration of many different kinds of time-stamped clinical data. The data needed to support bedside clinical decision making is generated in many departments throughout the hospital. Caregivers—including nurses, respiratory therapists, doctors, social workers, and physical therapists—all contribute a specific set of important clinical observations to the overall clinical data matrix.

Current hospital IS integrate critical clinical information and convey it to the caregiving team via a myriad of ways. Communication efforts are evolving, using both formal and informal methods, including charting on large paper flow sheets, printed laboratory reports, verbal reports, dictation, and handwritten/typed progress notes, to name a few. Interestingly, some of these methods that are paper based exist within a partially computerized system due to poor integration and virtually no interface capability between departments. Current practices using paper are notorious for being time consuming, illegible, and laborious. They are also error prone, allow only limited access (only one user can view at any one time), create storage nightmares, and have data redundancy. The problem is complicated because any new computer systems installed are often not able to integrate with the original or *legacy* systems, some of which were developed as far back as the 1970s. Thus, in many complex cases, the daily paper flow sheet creates a compact visual document that can be scanned in seconds for emerging and multisystem problems by experienced criticalists. Existing computer systems' screen displays require much clicking, rolling, and scrolling, which often obscures the temporal relationship of complex patient condition changes (*crashes*). Optimizing future systems with a higher level of integration and more cognitively appropriate and compact screen display would obviously work to correct many of these problems (Palma et al., 2012).

The ideal future method of communication would automate and integrate, in real time, all bedside monitoring information, laboratory results, medications, daily notes, alerts, reminders, and order entry directly into a centralized system. This centralized system would also have a decision support element that notices trends occurring in the patient, alerting the clinician, and recommending possible interventions. Additionally, this type of system provides data to hospital administrators so that optimizing decisions can be made regarding staffing, billing, materials management, and quality assurance, to name a few. This same system could also be used to push data to registries to assist hospitals with compliance mandates as well as in identifying the best treatment patterns.

To make the leap from current to future systems, hospitals are faced with hundreds of different products from which to choose. Prior to 1996, many of the larger products boasted they were a *complete system*, but they did not use standardized communication methods. The companies creating these products were unable to come to an agreement as to a unified common standard, and as a result, the government created laws and national standards in an attempt to mandate that a common communication standard be developed.

CONNECTIVITY STANDARDS AND THE HEALTH INSURANCE PORTABILITY AND ACCOUNTABILITY ACT

Background

The Health Insurance Portability and Accountability Act (HIPAA) of 1996 (P.L. 104–191, Title II, Subtitle F) is one of the largest pieces of healthcare legislation in U.S. history. According to

Friedrich (2001), HIPAA was passed with three main goals: (1) improve access to health insurance, (2) reduce fraud and abuse, and (3) increase the efficiency and effectiveness of the healthcare system. The initial goal of increasing accessibility is twofold. One aspect is related to making health insurance portable and continuous for those changing employment locations. The second aspect deals with deterring insurance companies from rejecting individuals with preexisting health conditions. Friedrich also explained that the second goal of HIPAA, related to fraud and abuse, and the third goal, related to increasing the efficiency and effectiveness of healthcare, fall under the Administrative Simplifications section of Friedrich (2001). The Administrative Simplifications involve the development of standards and regulations for accessing, transmitting, and storing medical data. Friedrich (2001) states that there are two broad types of regulations: standards related to electronic transmission of data and those intended to ensure the security and privacy of patient information.

The HIPAA mandated that specific code sets and computer communication strategies (both called *standards*) be decided and implemented by specific dates, now all past. The start dates for use of HIPAA-mandated coding and interconnection strategies were between 2003 and 2005. The foundational work for completing healthcare computer communication standards is in progress now. No one *standard* was, or is, completely finished. Standards-setting groups meet regularly. These groups are mostly voluntary. Overcoming the proprietary interests of vendors that have a large vested interest in proprietary (owned by the individual or company with restrictions on use) software, communication strategies, and clinical expression codes did require the federal HIPAA. New systems are required to be *HIPAA compliant*.

HIPAA Mandates: Codes Set Standards

Before HIPAA, there were no mandatory communication standards in place for healthcare providers and payers to transfer information electronically from one facility to another or from one facility to a payer. More than 400 different formats for electronic transactions had been created for communications between providers and health plans (Office of the Assistant Secretary for Planning and Evaluation [ASPE], 2000). HIPAA reduced the number to eight clinical code sets and two electronic transaction/computer communication standards for healthcare administrative and financial communications (ASPE, 2000). Congress made major operational modifications to the original plan in response to comments, problems, and evolving situations in May 2002 (U.S. Department of Health and Human Services [HHS], 2003).

Codes in HIPAA-defined healthcare rules are precisely formatted numbers and letters that match some clinical concept such as a diagnosis, medication, or treatment. Communication standards provide a specific place assignment where programmers insert needed coded information, such as a patient identifier, whether they are writing a lab system, a clinical system, or an administrative system.

The Health Level Seven International (HL7) and American Standards Committee (ASC) X12N computer communication standards provide a uniform programming structure, so different vendors of clinical, lab, or hospital IS can send medical and administrative information to each other, without data loss and with clearly defined meaning. The Fast Healthcare Interoperability Resources (FHIR) standards framework is a promising development that leverages web technology to access and exchange data across electronic systems (HL7, 2017).

A *code set* is any organized system of codes for listing data elements, such as tables of terms, or codes for medical diagnosis and medical procedures (HHS, 2003). Code sets, now defined under the HIPAA, are considered code set standards. Examples of these include the *International Classification of Diseases, Tenth Revision* (*ICD-10*); Healthcare Common Procedure Coding System (HCPCS); *Current Procedural Terminology* (CPT); *Code on Dental Procedures and Nomenclature* (CDT Code); and National Drug Code (NDC). The ICD-10-CM (*International Classification of Diseases, Tenth Revision, Clinical Modification*) is used for diagnoses and hospital patient services codes. Due to the American Recovery and Reinvestment Act (ARRA) of 2009, the Stage II Meaningful Use aspects of the HITECH legislation included converting from *ICD-9* to the more complex *ICD-10* by October 2014. To report supplies, durable medical equipment, and generic drugs under Medicare plans, HCPCS is employed (HHS, 2003). CPT is mandated for coding physician services. Dental services are coded under CDT, and NDC is used only for medications and drug systems for retail pharmacies (HHS, 2003).

Computer communication standards defined under HIPAA include ASC_X12N and HL7. ASC_X12N, Version 4010 (X12, n.d.) is used for health claims, attachments and encounters, payment and remittance advice, claim status, eligibility, referrals, healthcare enrollment, health plan premium payments, and first report of injury. This communication standard condenses more than 400 transaction formats, with one set of specific transaction standards that are formatted in one language (ASPE, 2000). HL7 is an accredited standards developing organization (SDO) that produces standards (sometimes called *specifications* or *protocols*) for a particular healthcare domain such as pharmacy, medical devices, imaging, or insurance (claims processing) transactions. HL7's domain is clinical and administrative data (HL7, n.d.).

As one can see, the elements defining the aforementioned code set standards are independent, not interdependent. Problems, therefore, quickly arose with initial attempts to apply HIPAA administrative code set standards to computerized clinical medical records. According to Chute (2002), most HIPAA approved code set standards, such as *ICD-9* and *CPT*, could lose more than half the underlying, detailed clinical information because these code sets were originally established for billing purposes. Loss of pertinent clinical details needed for bedside care and communication can be detrimental for the patient, the providers, and the institution. Because of the obvious need for standard vocabularies in the clinical setting (medical, nursing, and laboratory), the Office of the National Coordinator for Health Information Technology (ONCHIT) was established in late 2004 to coordinate these efforts (www.healthit.gov). The hoped-for outcome of these efforts is rapid development of complete clinical code set standards for care-based computerized patient records.

Different from the aforementioned HIPAA-defined code set standards, clinical code set standards in use are Systematized Nomenclature of Medicine Clinical Terms (SNOMED), Nursing Intervention Classification (NIC), Nursing Outcome Classification (NOC), North America Nursing Diagnosis Association (NANDA), and Logical Identifier Names and Codes (LOINC). "The SNOMED CT core terminology contains over 366,170 health care concepts with unique meanings and formal logic-based definitions organized into hierarchies" (SNOMED International, 2018). NIC, NOC, and NANDA are independent code sets used for nursing diagnoses, treatments, and outcomes documentation. Each of the three has issues such as an inability to combine and link unique concepts as a single concept, poor coding, and an inability to reduce concepts to an anatomic level. Informatics nurses are currently working to harmonize several terminologies so that nurses can document the nursing processes in a standard manner. Lastly, LOINC, which facilitates "One of the main goals of LOINC is to facilitate the exchange and pooling of results for clinical care, outcomes management, and research" (Logical Observation Identifiers Names and Codes, 2018).

HIPAA Mandates: Identifiers

Identifiers are numbers assigned to healthcare providers (individuals, groups, or organizations) that deliver medical services, other health services, or medical supplies. The final rule for the national provider identifier (NPI) was published in January 2004 (Centers for Medicare and Medicaid Services, 2005). The proposed rules for assigning unique identifiers to employers and health plans are, however, not yet fully operational. Employee identification numbers (EINs) are under scrutiny because the number to be used was determined by the Internal Revenue Service (IRS) to be the taxpayer identifying number, also known as the Social Security number (SSN). This was thought to be a good idea since most employees should already have an SSN assigned prior to being hired in an organization. The use of the SSN has, however, caused controversy because health information and financial information will be directly linked to the same number. Additionally, there are duplicate SSNs. National health plan identifiers (NHPIs) are also undetermined at this time (CMS, 2005).

HIPAA Mandates: Privacy

Before HIPAA, legal protection of patients' privacy and confidentiality was fragmented across state, federal, and commercial insurance systems, which left many gaps in patient privacy (Hebda, Hunter, & Czar, 2019). Evolving, implementing, and testing patient privacy rules under HIPAA is an ongoing process. The effective compliance date was April 14, 2003.

The Privacy Rule was constructed with hopes of protecting verbal, written, or electronic personal health information (PHI) that can be traced to an individual. This PHI refers to any record containing any of the 18 elements defined as personal health data (e.g., name, birth date, SSN, address). The rule protects PHI not only within the walls of the hospital but also while it is in transit to other locations (Friedrich, 2001). The rule applies to health plans, healthcare clearinghouses, and those healthcare providers who electronically conduct financial and administrative transactions (ASPE, 2001). Consent must be obtained from the patients prior to any release of their private information for treatment, payment, or other healthcare operations. Patients will have the right to restrict the use and disclosure of their information, and the option to file formal complaints if their privacy has been violated. All shared data must be stripped of PHI information unless sharing is authorized by the patient. In addition, patients must have full access to their medical records (ASPE, 2001). Since some of these elements are also vital statistics (e.g., date and time of birth) that are a matter of public record, and of extreme clinical importance for babies' healthcare management (e.g., developmental milestones), the problem for follow-up, other communication, and research is obvious to pediatricians. Since adults have no such issues, however, the situation in standards' setting groups is stalled, because vendors of adult systems would have difficulty and expense *retrofitting* their software to support the date/time aspect for neonates. Currently, progress toward full utility for neonates is slow and/or stalled.

HIPAA Mandates: Security

Security regulations refer to technical protection of computerized PHI transmitted electronically within and among provider and payer organizations. Security standards have three categories: (1) administrative security (e.g., access controls and contingency plans), (2) technical security (e.g., authorizations and audit controls), and (3) physical security (e.g., limit physical access to workstations; Hirsch, 2003). Although these three categories are different, the security measures proposed in each category require similar forms of intervention.

For clinical users, HIPAA has created a very unstable and tenuous balance between security and usability (Dawes, 2001). For example, many paper-based units have removed all charts from the bedside, including flow sheets, to keep the patient's data more secure. This poses a workflow problem, especially in an ICU, because that information is needed at the bedside. In computerized systems, excess security has become a burden because hospitals are requiring excessive password usage to gain access to EHRs. In an emergency this process tends to delay patient care when it is needed most. Log-in times range from 30 to 75 seconds in usual times, across most NICUs. A nurse accessing the computer for charting and so on may thus *waste* about an hour a day simply waiting for computer access.

HIPAA Mandates: Penalties

According to HHS, there are two types of penalties: civil and federal criminal (ASPE, 2001). For a civil penalty, the minimum fine for failure to comply with a standard is $100 per violation with a maximum of $25,000 for identical violations per year for each requirement violation. Criminal charges start at $50,000, with a maximum of 1 year in prison for wrongful disclosure (ASPE, 2001).

HIPAA Update 2013

HHS announced a final rule on January 25, 2013, that implemented a number of provisions of the HITECH Act to strengthen the privacy and security protections for health information established under the HIPAA. Since that time fines have been issued for violations of this rule.

Clearly, there are numerous layers of complexity when considering clinical IS. There are various types of IS available for all aspects of the delivery of patient care. When reviewing any IS, it is critical to consider if and how these systems communicate or integrate with one another. Whether the NICU is in the process of replacing an entire EHR, or a smaller change such as an automated flow sheet, it is important to use a formal process to evaluate options and select the system that is the best fit for the organization.

IS EVALUATION, SELECTION, AND IMPLEMENTATION

Bedside caregivers in the NICU need to have an understanding of general guidelines for evaluation, selection, and implementation of IS within their hospital organization. Bedside caregivers, not just administrative staff, must play an integral role in the extensive and elaborate process of hospital IS selection and installation. Bedside caregivers who interact with the clinical IS on a daily basis are called end users. End users help to define the requirements of the system in the early stages of evaluation and to give input during the selection process. End-user satisfaction is the key to the successful implementation of a system. A brief overview of these important processes follows, to ensure that modern-era bedside caregivers have an understanding of their roles and expectations during an NICU IS selection and implementation.

RESEARCHING IS SOLUTIONS

Many hospital organizations are either initiating the switch from paper-based charting systems to electronic charting systems or are moving from one electronic system to another. Some facilities currently have systems and are changing vendors, hardware, and/or

software. This type of project is a massive undertaking for a hospital—financially, logistically, and culturally. For future purchases, therefore, most hospitals are beginning to develop structured planning, purchasing, and implementation processes in an effort to avoid project failures.

The first stage in the system evaluation/selection process is to logically identify and list the problems with the current system in a structured format (e.g., a spreadsheet). It is important to research alternative technological solutions or enhancements to the identified problem(s). Often a multidisciplinary (IT, clinical, and administrative representation) approach to these early *brainstorming* sessions yields enough ideas to structure a more substantial search. Initially, a request for information (RFI) can be directed to vendors that specialize in clinical IS. The vendor will in turn reply with introductory product information. An RFI is a standard and affordable business process that is used to collect information about the capabilities of various products. The RFI is normally formatted so it can be used as an initial assessment tool for comparing vendors (Hunt, Sproat, & Kitzmiller, 2004).

Once the vendor list is at a manageable size, a more detailed comparison process begins, using a request for proposal (RFP). The main purpose of the RFP is to document the vendor's claims in terms of system functionality, support, training, cost, and implementation approach, including staff education and post-installation support plans for the early months of the *go-live*. The hospital's IT or IS department will likely compose this document with input from all affected parties. Some organizations elect to use an outside consulting firm to help with RFP development and system selection. At this step, input from the end users (practicing clinicians) is vital. An RFP should be created for each individual unit and should include its unique workflow issues. When you use an individualized approach, it is harder for the vendor to provide broad, generic solutions that may be technically capable, but do not really address the NICU's specialized requirements, and ultimately may be either unusable or unsafe, or both.

One of the most essential sections of the RFP describes the system's functional and technical requirements. Functional requirements are developed using input from bedside caregivers on the basis of the daily workflow needs and data management goals for the specific unit. These detailed requirements are listed by the requesting hospital in a table/database format. Technical requirements pertain to issues such as network and hardware specifications that are required to make the system run (Hunt et al., 2004). Vendor response columns should be provided so that the vendor can specifically address each requirement in terms of the technical details, defining how the system meets each specification. Each requesting hospital should provide a predetermined response key for the vendor to use. The preestablished response key assists the purchasing team in cross-vendor comparisons.

In addition to the functional and technical requirements, the implementation and maintenance plan for the proposed system should be requested of the vendor. In the RFP response, the vendor should provide, in writing, their plan for implementation, training, and support of the system (Hunt et al., 2004). These components can make or break the success of the system. Finally, the RFP should request a detailed cost matrix of all aspects of the vendor's system and its implementation, including costs, plans, and options for go-live testing and tuning and rollout staging.

The completed RFP is sent out to prospective vendors, and formal proposal replies are expected within weeks. If composed appropriately, the RFP will require the vendors to confirm that they meet the details of the request. Their responses will contain information that will allow a thorough evaluation and selection process.

EVALUATION AND SYSTEM SELECTION

As the vendor proposals are received, the informatics department and selection team will begin the evaluation process. A metric scoring scale can be applied to the objective sections of the submitted proposals. The objective sections include the functional, technical, and financial requirements. The scoring scale allows the hospital to evaluate the vendors' systems objectively and consistently. A numerical weight value will be assigned to each response. For example, a response of "Not available" should receive a weighted score of zero, whereas a response of "Available and already successfully installed in a similar healthcare facility" should receive the highest weight on the response key scale. All objective sections of each vendor's proposal are scored on the basis of his or her responses. Then a summary table can be created to display the final numeric results and ranking of each vendor.

Financial comparisons evaluate whether the requesting hospital can afford the high-scoring vendors. Typically, the financial department of the hospital assists in this phase. Several financial evaluation tools are commonly used. A cost–benefit analysis (CBA) is traditionally done by comparing the cost of each system with the proposed benefits. The CBA is, however, purely an estimation approach and incorporates such concepts as *intangible* benefits that are difficult to quantify for parallel comparisons. A second approach is a cost-effectiveness analysis (CEA), including a payback analysis, a return on investment (ROI) estimation, and a net present value (NPV) assessment. The ROI and payback analysis are both methods that determine the time for each system to repay its costs. Once a system pays for itself, cost savings for the hospital will begin. The NPV calculates the value of each system at any given time, thus determining the profitability in current dollars. Typically, the financial department performs these analyses. End users who are active in the selection process should be familiar with commonly used comparison methods.

Once the objective scoring is complete and the cost analyses are done, vendors should be ranked according to their scored percentages. This ranking acts as a consistent comparison tool to determine which vendor best meets the hospital's desired criteria. This process is important because the purchasing organization must be able to quantify necessary functions for their desired system.

Finalist vendors' products (usually two to three) can be further evaluated in many ways. Reference checks by telephone interviews of the specific vendor's clients to get an overall feel of client satisfaction with the vendor's installed system is one way to evaluate a finalist (Hunt et al., 2004). A standard questionnaire is another useful telephone tool that can again compare client feedback on an equal basis. There are several web-based agencies that conduct and publish results of satisfaction surveys for a fee that can be helpful to a buyer.

The next step is to organize on-site vendor demonstrations. Demonstrations are necessary for end users to test whether their functional requirements can actually be met. A demonstration evaluation test tool should be created to assess how each system functions in the context of actual daily workflow for the particular unit. Part of the tool should use test case scenarios that are unique to the unit and also taxing to a system. An example of such a scenario may be to "demonstrate the admission of unnamed triplets where two were born before midnight and one was born after midnight." The demonstration tool should also assess usability and functionality of clinical documentation. For example, "What happens if a nurse is documenting an assessment but gets called away from the bedside before finishing? Is his or her work saved and time stamped?"

The final step of product evaluation is to conduct site visits at other hospitals. Select similar hospital units that currently use the IS of interest. To obtain a true picture of how the system functions, it is best to conduct these site visits without the vendor present, which also allows the end users to express how they feel about the system and how it will fit into their workflow (Hunt et al., 2004). The site visit team should be multidisciplinary for gathering feedback from various perspectives, including different types of end users (i.e., nurses, respiratory therapists, doctors, informatics specialists). The site visit team should use the same evaluation tools that were used in the vendor demonstration to observe and evaluate the installed product function during real-life scenarios in real time. It is also important for the site visit team to note the physical layout of the unit and how the system fits into the staff's workflow. For example, is there a computer terminal in each patient room, or do the staff share one terminal per several patients? If the computers are mobile, do they easily fit into each patient room, or do the visitors have to leave before they can pass through the door? The site visit team can apply the on-site observations to their own NICU. In addition to environment and workflow observations, a site visit questionnaire can be created to gather more structured information from current end users.

As the evaluation process closes, a final decision-making team should review (a) subjective and objective information, (b) reference telephone interviews, (c) demonstration evaluation tool results, and (d) site visit feedback from questionnaires. Hospitals usually select a finalist and a runner-up vendor. The two finalist vendors' supporting information is presented to the project steering committee (i.e., the final decision makers.) This committee will likely include representation from high-level executives (CEO), financial personnel (CFO), nursing (CNO), medical (CMO), IS/Informatics (CIO), chief medical information officer (CMIO), chief nursing informatics officer (CNIO), and so on. Once the selection is made and contract negotiations are finished, the implementation phase will begin.

IMPLEMENTATION

The key to a successful system conversion (i.e., switching the old system out and bringing the new system in without clinical disruption) is a well thought out implementation plan. A project implementation team should include end-user representation from every shift, IT personnel, and vendor representation. Administrative representatives who are people-oriented problem solvers are valuable team members. End users who are bedside caregivers are integral to the installation process because they provide functional knowledge for both the system design team and the training team. IT team members can provide technical services and schedule planning tools to ensure a smooth transition. Team members from the vendor facilitate local customization efforts and training on the basis of their full understanding of their system's inner workings.

The implementation team is responsible for (a) educating themselves with 100% of the system's functions, (b) installing hardware and software, (c) customizing the system, (d) testing the system, (e) creating implementation and user documentation, (f) educating users hospital-wide, (g) overseeing the actual system conversion, and (h) conducting the post-implementation evaluation. Typically, the first five steps precede the live conversion. These steps make the system mesh with the subtle nuances of the hospital and/or the particular unit (i.e., the NICU). The last three steps rely heavily on end-user participation. The success of the system conversion is based on actual usability by the intended users in the clinical environment.

Before the installation of the hardware (monitors, keyboards, etc.) and software (instructions for the computer), the IT staff on the implementation team should verify the physical layout of the unit and check and supplemental power sources, lighting, noise, and privacy limitations. IT staff should walk through the unit with all end-user representatives while they visualize and verbalize issues unique to the unit. This step (*cognitive walkthrough*) helps prevent surprises and delays during the system-wide installation process.

Meanwhile, the system vendor representative responsible for implementation should initiate system education and training of the end users who are on the core team. The first end users trained will eventually become the trainers (Hunt et al., 2004). The end-user trainers need to know the operation of the system, its limitations, and backup plans in the event of an unexpected system shutdown. They must also understand how to log formal *issues and complaints* across all shifts to ensure continuous system quality improvement.

System customization, the third responsibility of the implementation team, ensures that the system is tailored to meet the unit's workflow needs. For example, the NICU may want to integrate the hospital laboratory list within the new system, so it can view the results of ordered laboratory tests and specifically and concisely check only *abnormal values* across a 60-patient census list. It is important for the implementation team to determine that all customization/modification requests are sensible. Sometimes the customization process becomes unrealistic as individual end users' desires expand. For example, one user may want to view vital signs with heart rate as the initial value, while another user may prefer the temperature first. A few systems reaching the market allow individual customization at this level, without changing the overall configuration for others. Currently, an entire NICU usually must form a consensus of how the standard data is to be represented. Keep in mind that many small modifications to the system usually are needed within the first 6 months of the installation. Expect to give the vendor reasonable time to make those changes.

System testing is a very important responsibility of the implementation team and the vendor, working together. As customization occurs, it is important to verify the system is working properly with the new changes. The testing should be carried out by members of the team not affiliated with the vendor. Each module of the system should be thoroughly tested for functionality using formal scenarios from actual clinical situations. Outlier management is important. Most NICU patients are *outliers* compared with the larger child and adult population. Thus, scenarios should include a sample of the most complex as well as common cases managed on the unit. Technically, the flow of data between modules should be verified and validated. System response times should be tested at peak volume of staff using the system simultaneously and should be monitored and tuned at intervals. Performance tends to degrade as use and data intensity increase over time. All system tests must be fully documented for historical and legal purposes.

As the system is being customized, modified, and thoroughly tested in the NICU, the implementation team begins to create and revise the system's documents. User guides and educational material are created during this phase. Typically, materials already supplied by the vendor will need to be updated/modified due to local changes made to the product. The hospital education department should be included at this phase to aid with hospital-wide training and 24/7/365 educational dissemination.

The hospital-wide end-user education phase should start a few weeks before the go-live (conversion) date. The users need to know what to expect of the system, the rollout, and the testing and tuning processes. They should feel prepared for the upcoming change. Choose several *super users,* who are computer savvy end users, who are eager to help roll out the new system, and who are liked and respected by colleagues. In terms of system training, a diffusion

approach tends to be the most successful. With the diffusion approach, super users, once trained, can train their coworkers with enthusiasm and during real-life scenarios/situations. It is best if the initial exposure to the system is in a quiet, comfortable, and well-lit area. Distractions should be kept at a minimum so that the training material can be fully absorbed. This session should not exceed 2 to 3 hours. If more time is needed, then subsequent sessions should be scheduled. After their exposure to the system, move the users to the patient care setting. After go-live (see the following paragraph), trainers should be available in the unit around the clock until the end users are comfortable navigating and using the system. Overtime pay for off-hours training builds positive attitudes.

When the implementation team has completed all planning, testing, documentation, and training steps, it is time for the final conversion or go-live step. There are several types of go-live options that have led to successful system conversions, including (a) parallel conversion, (b) pilot conversion, (c) phased conversion, and (d) big bang conversion. The parallel method involves running both the old and new system at the same time until the users are comfortable with the new system. This approach is time consuming and expensive, but is safe in terms of bridging documentation gaps. The pilot conversion involves changing only one unit at a time. This approach is timely and effective for some organizations. The phased conversion involves installing application modules individually throughout the hospital. This phased conversion takes a considerable amount of time, but may ease the users into the system at a more comfortable rate. The big bang approach involves shutting off the old system and turning on the new system overnight. This approach can be quite stressful for the end users and may lead to poor patient care. If the staff are adequately trained and are comfortable with the new system, however, this approach may be optimal, especially if the new system solves many preexisting problems. Each hospital should weigh the pros and cons of each approach heavily before choosing the best go-live scenario. Do not attempt massive inpatient conversions over holiday weekends, unless the hospital 24/7 critical care services can be closed down, or shifted to other hospitals for the duration.

There should be a post-implementation evaluation immediately and several months after the system conversion. Samples of the people directly involved in the conversion should provide feedback on the go-live process and on the system performance. This feedback may uncover gaps in the system use or performance. Structured feedback may also aid in the redesign of subsequent system conversion approaches. The post-implementation evaluation results should also be analyzed for operating costs, benefits, and system stability.

The implementation process requires careful planning and much work. Without a solid multidisciplinary implementation team the system conversion could fail, costing the hospital millions of dollars. The implementation team's stepwise responsibilities are critical to the ultimate success of the system. By following the eight aforementioned implementation guidelines, a hospital should be able to avoid pitfalls and complete a successful implementation.

FUTURE TRENDS AND NURSING IMPLICATIONS

Health IT is not yet at the point where data flows from monitors into the EHR documentation systems, synchronizing with all medical technologies and systems. Due in part to the HITECH Act, we now have information that can be analyzed to make predictions and improve patient care. For example, considering the current opioid crisis, with babies born with neonatal abstinence syndrome, how can we use predictive analytics to model an algorithm to predict when withdrawal is going to occur? Can we alert the bedside team in enough time to preempt the withdrawal from happening by medicating earlier?

McCartney and Drake (2016) offer an action plan for practitioner involvement with health IT. They suggest that nurses initiate an action plan, tackle current challenges, and transform practice.

SUMMARY

The intensive care environment has always depended on the most advanced technologies to care for patients. Traditionally, these technologies have been limited to bedside devices. It is inevitable that the device-based technology expand to include IS. Systems such as the electronic medical record are necessary to capture the data that these devices report throughout the ICU. With the help of advanced computer systems we can view and analyze patient data in ways that traditional paper-based methods cannot permit. As we evolve into the information age in healthcare, it is important that bedside caregivers have an understanding of the pros and cons of various types of IS, the importance of an integrated system, as well as the complexities that arise when implementing them within the NICU.

PARENT VOICES

Rosie Moore, DNP, RN

The specific gap in practice in the NICU is the challenge that parents face when they are discharged home. The underlying assumptions of these issues include a lack of confidence to be able to take care of the baby, not enough information to understand the machines, a lack of practice time, and increased readmission rates to the hospital within 30 days of discharge from the NICU. Regarding the population parents of premature babies, the argument that is most often heard from the nurses and the NICU team is that the parents have been in the NICU watching the nurses for the last 5 to 7 months and they should be able to take care of their infant (Hutchinson, Spillett, & Cronin, 2012).

The parents of premature babies have a higher stress level when the babies are discharged due to not receiving specific education to ease the transition home (Busse, Stromgren, Thorngate, & Thomas, 2013). In Miles and Huberman's

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(1994) study conducted via the patient reported outcomes measurement information system (PROMIS) following a discharge from the NICU, it was proved that there was a higher stress level for parents when they were discharged home. Premature infant readmissions were analyzed, and it was determined that there was a 31% readmission rate to the NICU. The parents needed to be taught skills on how to avoid a rehospitalization (Hutchinson et al., 2012).

Premature babies were being born daily with multiple medical conditions that carried on long term through the span of their lives. When they were transitioned to their homes, they required management of their special needs in the home setting. The transition program began 30 days before the baby was discharged to the home. If the teaching was not done prior to the discharge home, then when they went home, the baby was susceptible to errors made at home with medications, infection control, or treatment in general.

When a baby is taken home from the regular nursery it is noted to be a scary time for parents due to the newness of being a parent. For a parent of a premature baby, the anxiety increases, especially if the baby had a long NICU stay. The parents are accustomed to having the nurses there for support but when they go home, they feel alone.

The proposed solution for this gap in service is the implementation of an NICU navigator toolkit. The toolkit is designed to help hospital nurses, doctors, therapists, social workers, and parents communicate more effectively toward reducing the parents' anxiety surrounding their baby's discharge to the home. The presentation of the NICU patient navigator toolkit contains evidence-based studies and real-life examples to demonstrate the toolkit's necessity in the NICU.

References

Busse, M., Stromgren, K., Thorngate, L., & Thomas, K. (2013, August). Parent responses to stress: PROMIS in the NICU. *Critical Care Nurse, 33*(4), 1–13. doi:10.4037/ccn2013715

Hutchinson, S. W., Spillett, M. A., & Cronin, M. (2012). Parents' experiences during their infant's transition from neonatal intensive care unit to home: A qualitative study. *The Qualitative Report, 17*(23), 1–20. Retrieved from http://www.nova.edu/ssss/QR/QR17/hutchinson.pdf

Miles, M. B., & Huberman, A. M. (1994). *Qualitative data analysis: An expanded sourcebook* (2nd ed.). Thousand Oaks, CA: Sage.

ONLINE RESOURCES

Alliance for Nursing Informatics. Retrieved from https://www.allianceni.org

American Medical Informatics Association—Nursing Informatics Workgroup. Retrieved from https://www.amia.org/programs/working-groups/nursing-informatics

Health Information and Management System Society. Retrieved from https://www.himss.org

HealthIT.gov. Retrieved from https://www.healthit.gov/

Online Journal of Nursing Informatics. Retrieved from https://www.himss.org/ojni

The TIGER initiative. Retrieved from https://www.himss.org/professionaldevelopment/tiger-initiative

U.S. Department of Health and Human Services. Retrieved from http://www.hhs.gov

RECOMMENDED READINGS

American Organization of Nurse Executives. (2012). *Position paper: Nursing informatics executive leader*. Retrieved from http://www.aone.org/resources/informatics-executive-leader.pdf

Ball, M. J., Douglas, J. V., Hinton Walker, P., DuLong, D., Gugerty, B., Hannah, K. J., . . . Troseth, M. R. (Eds.). (2011). *Nursing informatics: Where technology and caring meet* (4th ed.). New York, NY: Springer-Verlag.

McCartney, P., & Barnes, J. (2012). *Perinatal nursing informatics guide for clinical health information technology*. Washington, DC: Association of Women's Health Obstetrics and Neonatal Nurses.

Nicoll, L. H. (Ed.). *CIN: Computers, Informatics, Nursing*. Hagerstown, MD: Wolters Kluwer Health.

Rikli, J., Huizinga, B., Schafer, D., Atwater, A., Coker, K., & Sikora, C. (2009). Implementation of an electronic documentation system using microsystem and quality improvement concepts. *Advances in Neonatal Care, 9*(2), 53–60. doi:10.1097/ANC.0b013e31819d4df4

REFERENCES

American Nurses Association. (2015). *Nursing informatics: Scope and standards of practice* (2nd ed.). Silver Spring, MD: Author.

American Recovery and Reinvestment Act. (2009). Retrieved from https://www.congress.gov/bill/111th-congress/house-bill/1/text

Centers for Medicare and Medicaid Services. (2005). *Promoting Interoperability*. Retrieved from https://www.cms.gov/Regulations-and-Guidance/Legislation/EHRIncentivePrograms/index.html?redirect=/EHrIncentivePrograms

Centers for Medicare and Medicaid Services. (2019) *Promoting interoperability (PI)*. Retrieved from https://www.cms.gov/Regulations-and-Guidance/Legislation/EHRIncentivePrograms/index.html

Chapman, A. K., Lehmann, C. U., Donohue, P. K., & Aucott, S. W. (2012). Implementation of computerized provider order entry in a neonatal intensive care unit: Impact on admission workflow. *International Journal of Medical Informatics, 81*(5), 291–295. doi:10.1016/j.ijmedinf.2011.12.006

Chute, C. G. (2002, November). *Medical concept representation: From classification to understanding*. Presented at American Medical Informatics Association Symposium, San Antonio, TX.

Collen, M. F. (1995). *A history of medical informatics in the United States: 1950's to 1990*. Indianapolis, IN: Hartman Publishing.

Dawes, B. (2001). Patient confidentiality takes on a new meaning. *AORN Journal, 73*(3), 596, 598, 600. doi:10.1016/S0001-2092(06)61954-6

Dudding, K. M., Gephart, S. M., & Carrington, J. M. (2018). Neonatal nurses experience unintended consequences and risks to patient safety with electronic health records. *CIN: Computers, Informatics, Nursing, 36*(4), 167–176. doi:10.1097/CIN.0000000000000406

Friedrich, M. J. (2001). Health care practitioners and organizations prepare for approaching HIPAA deadlines. *Journal of the American Medical Association, 286*(13), 1563–1565. doi:10.1001/jama.286.13.1563

Graves, J. R., & Corcoran, S. (1989). The study of nursing informatics. Image: *The Journal of Nursing Scholarship, 21*(4), 227–231. doi:10.1111/j.1547-5069.1989.tb00148.x

Health Information Technology for Economic and Clinical Health Act. (2009). *Title XIII of the American Recovery and Reinvestment Act of 2009 (Pub.L. 111–5)*. Retrieved from https://www.hhs.gov/hipaa/for-professionals/special-topics/hitech-act-enforcement-interim-final-rule/index.html

Health Level Seven International. (2017). FHIR overview. Retrieved from https://www.hl7.org/fhir/overview.html

Healthcare Information Management Systems Society. (2018). What is interoperatility? Retrieved from https://www.himss.org/library/interoperability-standards/what-is-interoperability

Healthcare Information Management Systems Society Analytics. (2018). *Electronic medical record adoption model*. Retrieved from https://www.himssanalytics.org/emram

Hebda, T., Hunter, K., & Czar, P. (Eds.). (2019). *Handbook of informatics for nurses and healthcare professionals* (6th ed.). New York, NY.: Pearson.

Hirsch, R. (2003). On HIPAA-the HIPAA security rule. *Healthcare Informatics, 20*(4), 56.

Hunt, E. C., Sproat, S. B., & Kitzmiller, R. R. (2004). *The nursing informatics implementation guide*. New York, NY: Springer.

Joski, A., Chyou, P., Tirmizi, Z., & Gross, J. (2016). Web camera use in the neonatal intensive care unit: Impact of nursing workflow. *Clinical Medicine & Research, 14*(1), 1–6. doi:10.3121/cmr.2015.1286

Kuperman, G. J., & Gibson, R. F. (2003). Computer physician order entry: Benefits, costs, and issues. *Annals of Internal Medicine, 139*(1), 31–39. doi:10.7326/0003-4819-139-1-200307010-00010

Logical Observation Identifiers Names and Codes. (2018). Retrieved from https://loinc.org/faq/basics/

Lowry, S. Z., Quinn, M. T., Ramaiah, M., Brick, D., Patterson, E. S., Zhang, J., . . . Gibbons, M. C. (2012). *A human factors guide to enhance EHR usability of critical user interactions when supporting pediatric patient care*. Gaithersburg, MD: National Institute of Standards and Technology. Retrieved from https://nvlpubs.nist.gov/nistpubs/ir/2012/NIST.IR.7865.pdf

McCartney, P. R. & Drake, E. E. (2016). Perinatal and neonatal health information technology: Past, present, and future. *The Journal of Perinatal & Neonatal Nursing, 30*(3), 209–213. doi:10.1097/JPN.0000000000000184

McGonigle, D., & Mastrian, K. G. (2018). *Nursing informatics and the foundation of knowledge* (4th ed.). Burlington, MA: Jones & Bartlett.

Mekhjian, H. S., Kumar, R. R., Kuehn, L., Bentley, T. D., Payne, B., & Ahmad, A. (2002). Immediate benefits realized following implementation of physician order entry at an academic medical center. *Journal of the American Medical Informatics Association, 9*(5), 529–539. doi:10.1197/jamia.M1038

Office of the Assistant Secretary for Planning and Evaluation. (2000). *Frequently asked questions about electronic transaction standards adopted under* HIPAA. Retrieved from https://aspe.hhs.gov/report/frequently-asked-questions-about-electronic-transaction-standards-adopted-under-hipaa

Office of the Assistant Secretary for Planning and Evaluation. (2001, May 9). *Protecting the privacy of patients' health information*. Retrieved from https://aspe.hhs.gov/basic-report/protecting-privacy-patients-health-information

Palma, J. P., Brown, P. J., Lehmann, C. U., & Longhurst, C. A. (2012). Topics in neonatal informatics. *NeoReviews, 13*(2), e81–e85. doi:10.1542/neo.13-2-e81

Saathoff, A. (2005). Human factors considerations relevant to CPOE implementations. *Journal of Healthcare Information Management, 19*(4), 71–78. Retrieved from https://www.himss.org/human-factors-considerations-relevant-cpoe-implementations-april-saathoff-rn-ms

Saba, V. K., & McCormick, K. A. (2015). *Essentials of nursing informatics* (6th ed.). New York, NY: McGraw-Hill.

Salanova, M., Llorens, S., & Cifre, E. (2012, June 25). The dark side of technologies: Technostress among users of information and communication technologies. *International Journal of Psychology, 48*(3), 422–436. doi:10.1080/00207594.2012.680460

SNOMED International. (2018). SNOMED CT. Retrieved from http://www.ihtsdo.org/snomed-ct

U.S. Department of Health and Human Services. (2003, February 20). *Health insurance reform: Modifications to electronic data transaction standards and code sets (45 CFR Part 162)*. Retrieved from https://www.federalregister.gov/documents/2003/02/20/03-3876/health-insurance-reform-modifications-to-electronic-data-transaction-standards-and-code-sets

X12. (n.d.). About ASC X12. Retrieved from http://x12.org/x12org/about/asc-x12-about.cfm

CHAPTER 40

Human Genetics and Genomics: Impact on Neonatal Care

Robin Dawn Clark

INTRODUCTION

Genetic disorders contribute significantly and disproportionately to the morbidity and mortality of newborns. Although congenital anomalies affect 2% to 3% of all newborns, they are present in 13% of infants admitted to intensive care units in developed countries. Chromosome anomalies and congenital malformations alone are responsible for 20% to 34% of infant mortality in the United States. About 10% of all live-born infants incur significant health consequences in childhood due to congenital anomalies, chromosome anomalies, neuromuscular and neurodevelopmental disorders, or intellectual disabilities (Toufaily, Westgate, Lin, & Holmes, 2018). Pathogenic variations in over 3,000 genes cause about 5,000 single-gene or Mendelian disorders that follow well-described patterns of inheritance. Online Mendelian Inheritance in Man is a curated and updated catalog of information about single-gene disorders (www.omim.org). More commonly, the accumulation of many small effects from the interplay of multigenic inheritance and environmental factors results in multifactorial traits that have a genetic component but usually do not follow Mendelian inheritance patterns. The true incidence of genetic diseases in the neonatal intensive care unit is unknown because ascertainment is incomplete.

In recent decades, remarkable improvements in genetic technology have reduced the cost and turnaround time for genetic testing and widened the scope of testing from the single gene to the genome. As these advances are implemented by clinical geneticists and other practitioners with expertise in their use, they have the potential to dramatically change the course of diagnosis and therapy for the sick neonate and expand the role of newborn screening for the well-baby. These advances improve the rate of diagnosis in infants with multiple congenital anomalies as well as in newborn babies with dysmorphic features, low birth weight, or neurologic impairment. Genetic analysis is now routine in infants with isolated birth defects and babies who feed poorly without explanation. This chapter summarizes commercially available genetic and genomic techniques, nomenclature, and vocabulary and provides a guide for the clinical application of these new technologies. Some definitions are provided but interested readers can also refer to the Talking Glossary of Genetic Terms maintained by the National Human Genome Research Institute at www.genome.gov/glossary/index.cfm.

GENETIC AND GENOMIC CONCEPTS AND TERMINOLOGY

A gene is the basic unit of hereditary information encoded in a sequence of nucleotides, composed of four bases (A for adenine, T for thymidine, C for cytosine, G for guanine) that make up the "alphabet" of DNA. In humans, over 20,000 gene pairs are inherited. Every child receives one copy of each gene from both parents: one copy of each gene in the egg and another copy in the sperm. Genes are composed of exons, sequences that are transcribed into RNA and then translated into proteins and introns, and noncoding DNA that separate exons and that are spliced out of the final RNA message. Intervening DNA sequences that separate genes actually make up the majority of human DNA. Noncoding DNA figures in the important and complex regulatory functions that control gene expression patterns in different tissues at different times. In humans, the nuclear genome refers to the totality of all 20,000+ genes, including all exons, introns, and intervening DNA sequences that separate the genes. The exome refers to the total of all coding regions, all exons, without intronic sequences or intervening sequences. Almost all genes are located in the nucleus, but specialized genes are located in the mitochondria; organelles that produce energy are located in the cytoplasm of the cell. Mitochondria have their own genome, which consists of multiple copies of circular DNA. They are exclusively transmitted from mother to child in the cytoplasm of the egg.

A specific version of a gene, an allele, can be common or rare. The Human Genome Project produced a reference map of the human genome, which is still being revised and amended as different populations are studied and more information about normal and abnormal genetic variation is gathered. When a gene sequence varies from the reference data, that change is called a variant. Common genetic variants that occur in 1% or more of the population are polymorphisms. Variants that cause disease, whether common or rare, are pathogenic, whereas variants that do not cause disease are benign. The status of some variants is unclear. A variant that is unique or about which little is known is called a variant of unknown significance (VUS). The status of a VUS can be revised as more information becomes available about its effects.

The phenotype is the outward or clinical expression of a genetic disease, whereas the genotype is the variation or change identified

in the genetic information responsible for that disease. The phenotype may not always be predicted from the genotype because a genetic variant may cause a disease in some but not all individuals who harbor it. Other genetic or environmental interactions may modify the phenotype. The lack of a genotype–phenotype correlation can make it challenging to interpret some genetic test results.

A genetic disorder is an autosomal trait when the responsible gene is located on one of the 22 numbered chromosomes or an X-linked trait when the responsible gene is located on the X chromosome. Few Y-linked genetic traits are associated with disease. Dominant traits are genetic disorders that are expressed when only one of the two alleles is pathogenic. These disorders may be familial, transmitted from a parent to a child across the generations, or sporadic and de novo, occurring for the first time in a family. A heterozygote has one normal (sometimes called wild-type) allele and one pathogenic allele. Affected individuals with a dominant trait have one pathogenic variant; they are heterozygotes. A recessive trait is expressed only when both alleles are pathogenic. Remember that genes themselves are not dominant or recessive; these terms apply to genetic disorders.

A careful family history is critical to the assessment of genetic disorders in the newborn. Family history information available in the maternal record is often copied and pasted into the infant's record to little effect, because the information gathered (about adult onset diseases, for instance) may not be relevant to the infant's problems. It is better to interview the family independently and ask questions pertinent to the baby's condition. Families may not volunteer information about a consanguineous relationship unless the question is put to them directly: "Could you and your partner be related to each other, from the same family?" Ask whether they have a grandparent or great grandparent in common, or whether they share a surname or come from a small isolated region. Ask about the health status of other offspring, living and deceased. Clarify the relationships between full siblings and half siblings. Ask about infertility and reproductive losses and most importantly whether other family members have been affected similarly to the baby. The family tree can be drawn out in a pedigree to visually represent the family members, usually through at least three generations. A list of symbols used to represent family members and instructions on how to draw a pedigree can be found at https://medicine.uiowa.edu/humangenetics/resources/how-draw-pedigree/instructions-how-draw-pedigree.

Unaffected individuals who have one copy of a pathogenic allele for a recessive trait are heterozygous carriers for that trait. Individuals who are affected with a recessive trait have two pathogenic variants: They are homozygotes when they have two alleles with the same pathogenic variant, which occurs in the majority of infants with sickle cell disease, and they are compound heterozygotes when they have two different pathogenic alleles, which often occurs in infants with cystic fibrosis. Both parents of a child with an autosomal recessive condition, such as cystic fibrosis or sickle cell disease, are almost always heterozygous carriers of a pathogenic variant in the responsible gene.

Males have one X chromosome and females have two. An affected male with an X-linked trait is hemizygous for the responsible pathogenic variant, whereas a female with one pathogenic X-linked allele is a heterozygote, because she also has one copy of a normal allele. Although females have two copies of the X chromosome, one copy is randomly inactivated in each cell. The inactive regions of the X chromosome do not express any gene products. X-chromosome inactivation is usually a random process and the ratio of the activity of the two X chromosomes is equal at about 50:50. However, occasionally, the ratio is skewed in favor of one or the other X chromosome. This explains why heterozygous carrier females sometimes express an X-linked trait, although when this happens the phenotype is usually milder than in affected males. Mild hemophilia in the mother of a boy with severe disease can be explained by the phenomenon of X-chromosome inactivation.

Gene expression can be modified by changes in chromosome structure that make genes more or less available for transcription. These epigenetic changes include methylation and acetylation that affect how tightly or loosely DNA is coiled around histone proteins. Tightly coiled regions of DNA are not actively transcribed. These epigenetic changes are influenced by environmental factors that can exert their effects during the formation of the egg or sperm, during pregnancy, and throughout infancy and early life. Exposure to adverse environmental factors in fetal life, such as malnutrition, pollution, environmental toxins, trauma, and stress, can alter the pattern of gene expression throughout life. Dr. David Barker proposed the Barker hypothesis, which traces the fetal origins of adult disease, such as obesity, coronary artery disease, and type 2 diabetes, to gene expression patterns set in motion by maternal malnutrition that produced low birth weight and other stressors in pregnancy. The socioeconomic implications of these effects can extend trans-generationally. Consider that a baby born today was conceived from an egg that was formed in her mother's ovary, when her mother was herself a fetus in the grandmother's womb. Thus, a grandmother's diet during her pregnancy decades earlier is expressed in epigenetic changes in the third generation and beyond.

Some chromosome regions are differentially methylated based on the parent of origin. These chromosome regions are imprinted with a methylation pattern that differs depending on whether it was laid down in an egg or a sperm. This maternally derived or paternally derived methylation pattern is maintained after fertilization and during each subsequent cell division. Usually the genes in the transcriptionally active regions are unmethylated, and the genes in the silenced areas that are not transcribed are methylated. About 50 imprinted genes within the differentially methylated regions on chromosomes 6, 7, 11, 14, 15, and 20 are expressed only from the actively transcribed chromosome from one parent. For instance, a microdeletion on chromosome 15q11.2 causes Prader–Willi syndrome when the deletion occurs on the paternally derived chromosome 15. Angelman syndrome, a different condition, results when the same region is deleted on the maternally derived chromosome 15. Uniparental disomy (UPD) refers to the situation in which both copies of a chromosome pair originate from the same parent. If the chromosome is an imprinted one, then some genes will not be expressed at all and others may be overexpressed. UPD can be caused by trisomy rescue. In this situation, a trisomic conception occurs, which makes the fertilized egg nonviable. However, during cell division, one of the three chromosomes is lost, and viability is restored with the correct number of chromosomes. However, when the lost chromosome came from the parent who contributed only one of the original three chromosomes, then the two chromosomes that remain both came from the other parent. This causes uniparental inheritance rather than biparental inheritance of a chromosome pair. When UPD is associated with advanced maternal age, trisomy rescue is the likely mechanism. Maternal UPD for chromosome 15, designated as matUPD15, causes Prader–Willi syndrome in about a quarter of affected children. UPD is always significant when it involves an imprinted chromosome region, but it can also cause genetic disorders when non-imprinted chromosomes are involved. This occurs when the parent of origin is also a heterozygous carrier of an autosomal recessive disorder. When that parent contributes two identical copies of the same chromosome (isodisomy) that contains the pathogenic allele, the child is

homozygous and affected. This explains the rare situation in which a child is affected with an autosomal recessive disorder but only one parent is a carrier.

PRENATAL SCREENING AND DIAGNOSTIC TESTS

When assisted reproductive technology is used to create embryos in vitro, the opportunity to screen the embryos for common chromosomal disorders, called preimplantation genetic screening (PGS), allows only those embryos to be selected for implantation that are most likely to result in a successful continuing pregnancy. However, this technique does not guarantee that the infant will have a normal chromosome complement at birth because only three to five cells are collected from the early blastocyst stage at day 5 of development. The biopsied embryos are frozen, and only some of them are used for implantation later. The fetus derives from the inner cell mass of the blastocyst, whereas the placenta and membranes derive from other regions. Therefore, the few cells that are obtained for PGS testing may not reflect the chromosome complement of the region from which the fetus eventually arises. Preimplantation genetic diagnosis is a similar technique that utilizes embryonic DNA to detect a particular genetic disorder for which the fetus is at risk.

Until recently, the offer of prenatal diagnosis was limited to high-risk pregnancies at risk for familial genetic disorders, those with confirmed fetal anomalies on ultrasound, and women of advanced maternal age, typically those who would be over 35 years of age at delivery, because of the known increased risk for fetal aneuploidy in this group. High-risk women were offered an invasive procedure, chorionic villous sampling (CVS) or amniocentesis for diagnostic testing of fetal or placental cells. The small risk for pregnancy loss, 1/200 to 1/500, following these procedures increased anxiety and decreased their utility.

Meanwhile, low-risk pregnant women were screened for congenital anomalies and aneuploidy. Detailed fetal ultrasound examination in the second trimester detected many, but not all, congenital anomalies. Screening for aneuploidy involved first- and second-trimester tests: a nuchal translucency measurement at 11 to 13 weeks gestation and first- and/or second-trimester maternal serum analysis of pregnancy-associated plasma protein A (PAPP-A), free beta–human chorionic gonadotropin (beta-hCG), alpha-fetoprotein (AFP), inhibin-A, and unconjugated estriol (uE3).

AFP levels are elevated in both maternal serum and amniotic fluid when a fetus has an open neural tube or abdominal wall defect. The relationship between low maternal serum AFP level and Down syndrome, which was recognized in the 1980s, was the basis for early maternal serum screening programs for Down syndrome.

A first-trimester screen (nuchal translucency, PAPP-A, beta-hCG) detects 85% of fetuses with Down syndrome at a 5% false-positive rate. The chance of Down syndrome (trisomy 21) is also increased when the second-trimester quadruple or quad screen reveals a pattern of low AFP and uE3 and elevated hCG and inhibin. The quad screen alone detects 81% of Down syndrome fetuses at a 7% false-positive rate. When first- and second-trimester maternal serum screens are integrated with a nuchal translucency measurement, the detection rate for Down syndrome increases to 95% with a 5% false-positive rate. Incorrect gestational dating reduces the efficacy of maternal serum screening because these analytes are reported as multiples of the median value for a given gestational age in an unaffected population (Ngo et al., 2018). Incorrect gestational dating can affect the interpretation of results by changing the comparison group to a younger or older fetal age. Other obstetric conditions such as multiple gestation or a deceased co-twin also complicate the interpretation of the analytes.

Trisomy 18 is associated with a high likelihood of fetal congenital anomalies on ultrasound and low AFP, low hCG, and low uE3 in the second-trimester maternal serum screen. In the absence of fetal chromosome anomalies, abnormal maternal analytes (low PAPP-A and low free beta-hCG in the first trimester, and low estriol and high AFP, hCG, and inhibin in the second trimester) are associated with adverse obstetric outcomes including prematurity, fetal demise, miscarriage, preeclampsia, and low birth weight (Harris, Reed, & Vora, 2018).

The prenatal testing paradigm shifted early in the 21st century, when noninvasive prenatal screening tests (NIPS/NIPT) for aneuploidy became commercially available (Renga, 2018). NIPS/NIPT offers higher detection rates for the most common fetal aneuploidies than screening with maternal serum analytes. While NIPS/NIPT cannot replace amniocentesis and CVS, it has drastically reduced the need for invasive diagnostic testing in the unaffected fetus. NIPS/NIPT analyzes small cell free DNA (cfDNA) fragments derived from the fetus that are normally present in the maternal circulation during pregnancy. Fetal cfDNA, which is present in maternal supernatant, is derived mostly from the normal degradation of trophoblasts in the placenta. It accounts for 10% to 15% of all cfDNA in maternal serum. The amount of fetal DNA is compared with that of the maternal DNA, which is present in both the supernatant and the white cells that make up the Buffy coat. Several techniques for analyzing cfDNA are employed by different laboratories. One common method assesses the relative amount of DNA contributed by the chromosomes of interest to the total amount of fetal DNA with a high degree of accuracy; a variation in the expected ratio is an indicator of the risk of aneuploidy. The results are not reliable when the fetal fraction, which is the proportion of total cfDNA that derives from the fetal placenta, is 4% or less. This is more common in obese women in whom the turnover of adipose tissue contributes to the higher maternal fraction of cfDNA.

Although the best screening parameters with cfDNA testing for the aneuploidies are achieved for Down syndrome (trisomy 21) with a detection rate of 99.7% and a false-positive rate of 0.4%, the clinical significance of a positive test for an individual patient varies with the prior (pretest) probability of fetal aneuploidy. It is less predictive for young mothers and becomes increasingly predictive as the maternal age increases. In the general obstetric population, a low-risk group, the positive predictive value (PPV) of a cfDNA test with an abnormal Down syndrome (trisomy 21) result ranges from 45% to 76%. A PPV calculator is available at www.perinatalquality.org/vendors/nsgc/nipt. For this reason, NIPS/NIPT must be considered a screening and not a diagnostic test, and abnormal results should always be confirmed. False-negative results for Down syndrome (trisomy 21), which are rare, can often be explained by mosaicism for a normal chromosome cell line in placental tissue. Fetal cfDNA testing for sex chromosome aneuploidy can be confounded by undiagnosed sex chromosome aneuploidy or mosaicism in the mother.

Professional guidelines for the use of cfDNA testing in pregnancy have evolved beyond high-risk pregnancies (women aged 35 years and older, pregnancies with documented fetal congenital anomalies). Now women may choose cfDNA testing regardless of their risk status, although testing in certain situations, such as multiple gestations and pregnancies conceived with donor eggs, is not recommended because it is less reliable. Testing options have expanded to include common microdeletion syndromes and some genetic disorders (Shaffer & Norton, 2018). In the future, cell-free RNA tests may be able to assess gene expression patterns in

mother and fetus and predict preterm delivery, preeclampsia, and other obstetric and neonatal complications.

NEWBORN SCREENING

Newborn screening tests are performed on infants within the first days of life to detect serious health disorders presymptomatically and prevent avoidable health problems. The prototypic newborn screening test, the Guthrie test, was implemented in the mid-1960s to detect phenylketonuria, an inborn error of metabolism that was successfully treated with dietary protein restriction. After blood from a heelstick was applied to circles on a filter paper card, the dried blood spots were sent to a regional laboratory. Discs punched out from the dried blood spots inhibited bacterial growth when the phenylalanine level was elevated in the sample. This simple concept has evolved in scale and complexity to detect over 50 conditions. In the 21st century, tandem mass spectrometry (MS/MS) and related techniques have expanded newborn screening test algorithms to detect a great number of abnormal molecules with the first- and then second-tier analysis (Ombrone, Giocallere, Forni, Malvagia, & la Marca, 2016). Hearing loss, hypothyroidism, congenital adrenal hyperplasia, hemoglobinopathies, cystic fibrosis, organic acidopathies, amino acidopathies, fatty acid oxidation disorders, and dozens of other metabolic disorders are now routinely included in newborn screening programs.

Each newborn screening test algorithm has a different sensitivity and specificity rate, designed to detect affected infants, but false-positive and false-negative results occur for all diseases that are screened. False-positive newborn screening tests for aminoacidopathies are common in premature infants and babies fed with elemental formulas or total parenteral nutrition. When retested later, after the babies are feeding regular formula by mouth, the repeat results are usually negative. However, it should never be assumed that a positive test in a premature infant is falsely positive. Always complete a repeat test when advised to do so. Similarly, a normal newborn screening test reassures but it does not guarantee that the child is unaffected. A small percentage of newborn screening tests are falsely negative. In California, for instance, newborn screening for cystic fibrosis fails to detect about 5% of affected infants who have two rare pathogenic alleles in the *CFTR* gene.

In successful newborn screening programs, timely and accurate laboratory results are supported by a robust program of patient and medical provider education, prompt and efficient clinical follow-up of abnormal results, and responsive program administration and development. Public health agencies vary in their ability to deliver high-quality newborn screening programs due to challenging social, economic, health, and political environments in which they operate. Lack of government support limits the success of newborn screening in many developing regions of the world. Although legally required in the United States, newborn screening is fee-based in some states, which may limit utilization. Newborn screening is less effective when blood is collected too early or in quantities insufficient to complete the analysis, when infants are born outside of the hospital system, or when babies are discharged early from hospitals. Measuring the efficacy of newborn screening programs is hampered by differences in data collection and program design between and even within countries, as different states and provinces maintain their own budgets and infrastructure.

There is no agreed universal newborn screening policy. Throughout the world, newborn screening programs are heterogeneous and lack consensus (Therrell et al., 2015). In the United States, the U.S. Congress passed legislation supporting national screening efforts that was signed into law in 2008. This created a Secretary of Health and Human Services Advisory Committee on Heritable Disorders in Newborns and Children. This committee has worked with the American College of Medical Genetics and Genomics (ACMG) to develop a Recommended Uniform Screening Panel (RUSP; www.hrsa.gov/advisory-committees/heritable-disorders/rusp/index.html) of 32 conditions that now include severe combined (T-cell related) immunodeficiency syndromes, critical congenital heart disease, and the lysosomal storage disorder (Pompe disease). Other diseases are being nominated for inclusion in the RUSP as treatment becomes available or as the cost of detection is reduced. Laboratory screening methods for X-linked adrenoleukodystrophy, Fragile X syndrome, and spinal muscular dystrophy are being developed and tested. In the future, newborn screening may adopt a genomic approach.

CHROMOSOMAL ANALYSIS

Chromosome anomalies affect about 1 in 150 live-born infants, but not all of them will be detected in the newborn period. The first step in conventional chromosome analysis is tissue culture. Intact cells are cultured over several days to stimulate cell division. Typically a blood sample is collected and the white cells or lymphocytes are cultured in the cytogenetic laboratory, but any viable tissue type can be analyzed including amniotic fluid cells (amniocytes), placental tissue, bone marrow, and skin biopsies (Malam et al., 2017). After these cells have been coaxed into dividing, the cell division process is arrested during metaphase when the chromosomes have condensed in the nucleus and are visible under the microscope. The matching chromosomes that make up a chromosome pair are homologs. These 23 individual chromosome pairs can be identified by their size and unique banding patterns after staining with Giemsa. An experienced technologist then photographs the chromosomes, evaluates their morphology, and arranges them from largest to smallest in an ordered display of all chromosome pairs, which is called a karyotype. Results are reported with the chromosome number first, followed by the type and number of sex chromosomes, for example, 46,XX and 46,XY. Euploidy refers to the correct number of chromosomes (46), referring to the 22 numbered chromosome pairs and the sex chromosomes, XX or XY. Aneuploidy refers to any other number of chromosomes. Monosomy refers to the absence of one chromosome from a chromosome pair. Turner syndrome is caused by the lack of a second sex chromosome. Monosomy X refers to a 45,X chromosome complement. Similarly, trisomy 21 refers to an extra copy of chromosome 21 in every cell, causing Down syndrome, and is written as 47,XX, + 21. Triploidy refers to the addition of a complete extra set of chromosomes in every cell (69,XXX or 69,XXY or 69,XYY).

With some miscalculations along the way, the chromosome pairs were numbered from largest (chromosome 1) to smallest (chromosome 22 was mistakenly thought to be the smallest, but in fact chromosome 21 is smaller). The short arm of the chromosome is oriented up, toward the top of the page, and is referred to as the p arm. The long arm of the chromosome, oriented down toward the bottom of the page, is the q arm. The centromere separates the p and q arms and provides the microtubular attachment site for each chromosome during cell division. Light- and dark-stained bands are numbered from the centromere out to the tip or telomere. The lower the band number, the closer to the centromere. Longer chromosomes have more visible bands. Del refers to a deletion and dup refers to a duplication of chromosome material. Acrocentric chromosomes (13, 14, 15, 21, 22) have centromeres placed nearer to one end, with vestigial short arms that are highly variable in size and contain few genes. A Robertsonian translocation occurs when

two acrocentric chromosomes have lost most or all of their short arms and fused, long arm to long arm, at their centromeres to produce a derivative chromosome (designated der). A Robertsonian translocation can involve chromosomes within the same acrocentric chromosome pair; for instance, an unaffected female carrier whose pair of chromosomes 21 have joined together would be denoted as 45,XX,der(21;21)(q10;q10). It can also occur between different acrocentric pairs, such as in 46,XY, + 13,der(13;14)(q10;q10), indicating an affected male individual with three copies of chromosome 13, one of which is a derivative chromosome composed of the long arms of chromosomes 13 and 14 (in addition to two free-standing copies of chromosome 13). A reciprocal translocation involves breakage in chromosomes from different chromosome pairs, swapping of the broken pieces between them, and reunion of the chromosome fragments to form two (or rarely more) derivative chromosomes. A reciprocal translocation is designated first by a lower case t, followed by the numbers of the affected chromosome pairs in the first set of parentheses, followed by their respective breakpoints in another set of parentheses, for example, 46,XX,t(5;12)(q11.2;p13). Reciprocal translocations are balanced, when all chromosome material is present, or unbalanced, when only one of the two derivative chromosomes is present. Conventional chromosome analysis is the only test that confirms the number and morphology of individual chromosomes and identifies structural chromosome rearrangements such as inversions, translocations, and rings. The method is time-consuming and requires a high degree of expertise. Finally, and most importantly, the resolution is limited by what the human eye can see with a microscope, making this test less sensitive for the detection of small deletions and duplications of 10 megabases (Mb) or less. Chromosome analysis is no longer the preferred first-line diagnostic test for infants with congenital anomalies. However, it is still the preferred test when Down syndrome, Turner syndrome, or a balanced translocation is suspected.

Fluorescence In Situ Hybridization

Fluorescence in situ hybridization (FISH) testing identifies the number of copies of specific DNA regions that bind with a single-stranded DNA probe that contains a fluorescent marker, which makes it visible under the microscope. Rapid FISH test results are available within a few hours. Because dozens or hundreds of individual cells can be scored quickly, this is a useful technique for detecting mosaicism, when there are two or more cell types such as 45,X/46,XY. FISH is the preferred first test when trisomy 13 or trisomy 18 syndrome or sex chromosome aneuploidy is suspected. FISH tests require intact cells and prior knowledge of the region of interest.

Microarray Analysis

G-banded chromosome analysis detects discrepancies in chromosome number, size, or banding pattern by directly visualizing chromosomes in the metaphase nucleus of intact cells using a microscope. A major disadvantage of this method is that structural changes must be at least 3 to 10 Mb in size to be detected. Chromosome microarray analysis (CMA) utilizes DNA-based techniques to detect much smaller chromosome microdeletions or duplications. Because microarray is able to detect smaller chromosomal variations that are beyond the resolution of microscopy, it produces a diagnostic yield that is about 10% higher than conventional G-banded chromosome analysis (Ronan, 2018).

The first step in this process is the extraction of DNA from the intact cell. Small pieces of the patient's DNA are hybridized to a target, or array, that contains a reference sample of DNA from all the chromosome regions of interest. By comparing the patient's DNA with the reference sequence, a chromosome microdeletion or microduplication can be detected with much greater sensitivity than with conventional chromosome analysis, which is limited by the resolution of the human eye and the magnification power of a microscope. By analyzing these small pieces of DNA, microarrays detect copy number variants (CNVs) at the level of the chromosome. They do not detect DNA sequence variants. The chromosome microarray is the first-tier test for the infant with congenital malformations or dysmorphic features (Bachman, DeWard, Chrysostomou, Munoz, & Madan-Khetarpal, 2015). Easy to understand information about many rare CNVs and numerical chromosome anomalies, appropriate for both families and medical professionals, is available at www.rarechromo.org.

Microarray Nomenclature

Microarray and chromosome abnormalities are described using the International System for Human Cytogenomic Nomenclature, which is regularly updated, most recently in 2016. Normal microarray results indicate that the expected chromosome pairs are present in two copies. Normal female and male results are reported, respectively, as arr(1-22,X)x2 or arr(1-22)x2,(X,Y)x1. Abnormal microarray results are expressed in terms of the genomic position of the copy number change within a specific version of the genomic map. Over 3 billion nucleotides in the human genome have been assembled into a map, but this map continues to be refined and updated with new revisions. Not surprisingly, reference points change with different versions. Microarray results refer to the version of the human genome map that was used to generate the coordinates that are being reported, usually in hard brackets: [hg19] for human genome map 19 or [GRCh38/hg38] for Genome Reference Consortium Human Genome Build map 38. The map version is followed by the chromosome bands for the region involved. This is followed by two 9-digit (usually) numbers, separated by a dash, and enclosed within a set of parentheses, followed by the times symbol ("x") and the number of copies identified. For example, arr[hg19]4q32.2q35.1(163146681-183022312)x1 describes a deletion of the long arm of chromosome 4 from band 4q32.2 to 4q35.1, using coordinates from Human Genome map 19. The large numbers refer to the genomic position of the nucleotides that mark the start and stop positions of the CNV. The length of the CNV can be determined by subtracting the smaller parenthetical number from the larger one: in this case, the deletion size is 19.8 Mb (1 Mb = 1,000,000 nucleotides). By inputting the map version, chromosome number, and genomic coordinates into a genome browser, a list of genes within the CNV can be obtained. This genome browser is maintained by the University of Miami (http://firefly.ccs.miami.edu/cgi-bin/ROH/ROH_analysis_tool.cgi).

Using Microarray and Conventional Chromosome Analysis

CMAs have become the first-tier test replacing conventional chromosome analysis in most cases and especially in the evaluation of infants with multiple congenital anomalies of unclear etiology. However, there are some structural anomalies that can only be detected with conventional chromosome analysis. Although there are various microarray techniques, all of them analyze small pieces of DNA rather than intact chromosomes. This means that chromosome morphology, including structural anomalies such as inversions and balanced translocations, cannot be assessed with microarrays. Chromosomal mosaicism, in which there are two or more cell lines with differing chromosome complements, may not be detectable with CMA.

Both techniques have advantages and disadvantages, and neither test can detect all types of chromosome abnormalities. Bi et al. (2013) compared the effectiveness of conventional chromosome analysis and CMA, which when performed simultaneously in 3,710 consecutive patients identified a smaller number of abnormalities that were detected only with one of the two techniques. About 1% of patients with a normal CMA test had a chromosome abnormality that was detected with conventional chromosome analysis. The chance of missing an abnormality is low if CMA is the first-line test, but when clinical suspicion is high, chromosome analysis should be considered even when the CMA test is normal.

For some indications, such as suspected Down syndrome (trisomy 21), conventional chromosome analysis is the preferred test because the main objective is distinguishing between trisomy 21 in which there is an extra chromosome 21 (and 47 chromosomes) and a low risk of recurrence, or a translocation involving an extra copy of chromosome 21, which can be familial with a higher risk of recurrence. The microarray detects an extra copy of chromosome 21 in the patient with Down syndrome (trisomy 21) but does not distinguish between these two types. For the indication of recurrent miscarriage, in which the concern is that one member of the couple may have a balanced translocation, chromosome analysis is the method of choice. There are also situations when both tests are needed to clarify the nature of a complex chromosome anomaly.

CNVs and Other Microarray Abnormalities

The human genome tolerates quite a bit of variation and many healthy, apparently normal people have benign CNVs. The clinical significance of CNVs is an area of active clinical investigation. When a CNV of unknown clinical significance is identified in a child, parental studies are often recommended. As a general rule, microduplications are more often benign and tolerated and microdeletions are more likely to be pathogenic and disease causing. Regions of the genome that are studded with repetitive elements or inversions can become error-prone because it becomes difficult for chromosome pairs to line up exactly side by side during the formation of the egg or sperm, when chromosome material is normally exchanged between homologs. These regions are the sites of recurring CNVs such as the deletion of chromosome 22q11.2 associated with conotruncal cardiac defects and cleft palate or the deletion at chromosome 15q11.2 that causes Prader–Willi syndrome.

The clinical significance of a CNV may not be clear if it is small or unique, without precedent in the medical literature. Some CNVs have to be investigated further to determine their significance. The recommendation is often made for parents to be tested for the same CNV found in their newborn. CNVs that are de novo, occurring for the first time in the egg or the sperm during gametogenesis rather than inherited from a parent, are more likely to be pathogenic. This is how a CNV can occur for the first time in a family. A familial CNV that is present in an unaffected parent or sibling is less likely to be pathogenic.

Rarely, an affected parent transmits a familial pathogenic CNV to his or her child or an unaffected parent has a mixture of affected and unaffected cells and is mosaic for the trait. Typically, parents are tested with a blood sample. A normal result is reassuring; however, it may not be adequate to detect low-level mosaicism in blood or mosaicism that is confined to another tissue, including gonadal tissue. An unaffected parent with a normal blood test for the CNV identified in his or her child still has a small residual risk to be a gonadal mosaic for the CNV, and this confers a small risk of recurrence for a similarly affected child in a future pregnancy. Hence, genetic counseling and prenatal diagnosis in future pregnancies are offered to families after the birth of an affected child with a CNV, regardless of the parental testing results.

The single-nucleotide polymorphism (SNP) microarray technique evaluates thousands of common SNPs that are present in the genome. SNPs vary between individuals and do not cause disease. Most individuals have inherited different SNPs from each parent, making them heterozygous for some SNPs and homozygous for others. By comparing the two SNP alleles at thousands of SNP sites throughout the genome, SNP microarrays can detect regions of homozygosity (ROHs), in which the same SNPs are present in both alleles for long stretches of the DNA sequence. When an ROH, also called a region of loss of heterozygosity (LOH), is confined to one chromosome or a chromosome region, it may be caused by UPD. When both the size and the number of regions of LOH are large, they indicate consanguinity, a familial relationship between the parents, such as first cousins, which is common in many cultures around the world. When the regions of LOH are fewer or smaller, a more distant relationship based on shared ethnicity or a distant common ancestor is more likely. More significantly, when regions of LOH make up a major component of the total DNA, an SNP microarray can identify an incestuous relationship between the parents. In the context of incest, especially when the mother is a minor, the possibility of sexual abuse by a male relative could be the basis of a broader investigation by police, social services, or child protection agencies.

GENE AND GENOME TESTING

Most pathogenic genetic variation is present in the coding sequence of genes, and genetic testing focuses on sequencing the nucleotides that make up exons and intron–exon boundaries (Berg et al., 2017; Petrikin et al., 2018). The original method for gene sequencing, and still considered the most accurate, the Sanger sequencing method, is time-consuming and expensive. It requires isolating the genetic material to be sequenced first and then separating and ordering the sequence fragments that are generated from the smallest to the longest, based on the identity of the final nucleotide. Even after automation improved the efficiency of this technique, it was too slow and costly for large-scale gene analysis. The so-called next generation sequencing (NGS) techniques reverse the Sanger workflow by sequencing many genetic fragments first, and then matching the sequencing products, called "reads," which are of varying lengths and with variable overlaps, to a reference sequence afterward (Boemer et al., 2017). There is not one but many NGS techniques, and all of them rely on massive parallel sequencing of many different genetic regions at the same time and powerful computational algorithms that process large amounts of complex data to complete the analysis. Using NGS techniques, large panels of genes can be sequenced at the same cost and turnaround time as a single gene could be analyzed using the Sanger method. The quality of NGS sequencing is less robust than Sanger sequencing, but the difference is small. Nevertheless, the quality of NGS sequencing data can affect the interpretation of results. These data are critical for accurate interpretation of results: how many exons are captured by the test, the number of times each nucleotide is sequenced (the number or "depth" of reads), and the sensitivity of the computer algorithm that is used to identify variant signals or "calls" and interpret them. A low read-depth increases the chance that only one allele was sequenced or "read" several times rather than both. NGS techniques may not reliably detect a mosaic pathogenic variant. Some variants that are located deep

within introns may not be detected at all because these techniques focus on exonic variants.

The ACMG recommends using standard terminology for the interpretation of DNA variants: pathogenic, likely pathogenic, VUS, likely benign, and benign. The interpretation of a variant can change over time as more information becomes available about its pathogenicity.

Certain types of pathogenic variants, such as gene rearrangements, deletion or duplication of a single exon, or expansion of regions with runs of triple-nucleotide repeats (e.g., increased numbers of CGG repeats in Fragile X syndrome), are not reliably detected with NGS techniques. Special deletion/duplication testing, such as multiplex ligation-dependent probe amplification, should be considered when sequencing does not detect a pathogenic variant in a patient with a convincing phenotype. Methylation-sensitive sequencing test detects genes that are silenced by hypermethylation.

EXOME AND GENOME SEQUENCING

Exome sequencing, which includes all exons from the human genome, is the ultimate gene panel. The exome encompasses about 1% of the human genome but captures about 85% of the pathogenic variants (Borghesi et al., 2017; Hayward & Chitty, 2018; Meng et al., 2017). The test costs thousands of dollars and takes weeks to months to return results. The detection rate varies from 25% to 40% depending on the phenotype. Higher detection rates can be achieved by including tissue samples from both parents, known as a trio test, to act as comparators. The informed consent process is extensive because parents need to be aware of the chance of detecting variants of unknown significance, results that are inconsistent with the child's phenotype, or unanticipated significant pathogenic variants unrelated to the phenotype, such as a cancer predisposition trait, that could affect one of the parents.

The more extensive genome sequencing test, which includes all coding and noncoding DNA, offers a higher detection rate at a higher cost. New rapid techniques for trio whole genome sequencing are being investigated in randomized controlled trials for accelerated diagnosis in critically ill infants where they show improved rates of diagnosis in selected populations of infants.

CHALLENGES OF INTERPRETING GENETIC OR GENOMIC TESTS

When results are clear-cut, either pathogenic or benign, and the pathogenic variants are associated with a phenotype that matches the patient's features, genetic testing can enhance medical care and family genetic counseling, eliminate unnecessary testing, and provide timely information and support (Lalani, 2017). However, this scenario is not universal. Some genomic test results are uninformative or equivocal or do not correlate with the patient's phenotype. Genetic tests can be difficult or impossible to interpret when the patient's phenotype has not been adequately defined.

Sometimes even extensive testing reveals only one pathogenic mutation in an autosomal recessive trait that matches the patient's phenotype. In this situation, the challenge is to identify the second pathogenic variant with another testing modality. Sanger sequencing, deep intronic sequencing, and/or specialized deletion/duplication testing can be considered in those situations. Sometimes a nongenetic test can confirm the diagnosis even when genetic testing cannot detect the second variant. For instance, a positive sweat test confirms the diagnosis of cystic fibrosis in a symptomatic child in whom only one variant in the *CFTR* gene can be detected (Rosenfeld, Sontag, & Ren, 2016).

As more genes are tested, the likelihood of finding one or more VUSs increases. VUSs are time-consuming to evaluate and difficult to interpret. They cannot be ignored because they may hold the clue to a diagnosis but neither can they be relied upon as evidence of a diagnosis. Family testing and careful examination of the parents and other relatives are needed to establish a relationship between the presence of the VUS in a family member and any associated phenotypic features. This clinical information should be shared with the laboratory that performed the testing. Over time, the laboratory may update the status of a VUS to benign or pathogenic as more information about the gene variant, its population frequency, and associated phenotypes becomes available. In the meantime, VUSs should not be considered diagnostic, and they should not be used for prenatal testing or presymptomatic testing. Secondary findings, also called incidental findings, in genes unrelated to the original phenotype must be shared with the family if they are of medical consequence. Such pathogenic variants may put a parent or other relative at increased risk for a disease and possibly increase anxiety about their own health.

Optimizing Utilization of Genetic Testing

Although faster and cheaper gene sequencing offers many advantages, it does not inevitably lead to improved clinical care. There are thousands of genetic tests to choose from, and new genetic tests are entering the market every day. Clinicians may misuse or overuse genetic tests because of the relative ease of ordering a blood test and the time it takes to order the correct test. Larger gene panels or exome tests are not always the preferred testing strategy. Limited genetic testing for a known familial variant can be performed in a way that significantly reduces costs by ordering a targeted test for that particular gene variant rather than ordering the same large gene panel that was used to identify the variant in the index case (Geddes, Basel, Frommelt, Kinney, & Earing, 2017). Choosing the best test can be difficult even for experts in the field. Some hospital laboratories are employing genetic counselors to review genetic test orders, whereas others are implementing best practice guidelines or contracting with genetic case management consultants to optimize utilization of genetic testing. Genetic laboratories, genetic counselors, and insurers are working together to optimize utilization through professional engagement at Patient-centered Laboratory Utilization Guidance Service (PLUGS; http://www.schplugs.org/).

Choosing the Best Person in the Family to Test

Genetic testing is more meaningful when a pathogenic variant is identified first in an affected person. Then subsequent relatives who test negative know that the variant in their family is detectable with the technique that is being used. However, when the genetic testing process begins with an unaffected person, a negative test is uninformative and cannot be used to counsel that person that his or her risk of disease is reduced, because the pathogenic variant has not been identified and may in fact not even be present in the gene that is being studied. It is always best to start genetic testing with an affected person rather than an unaffected one.

Finding a Genetic Testing Laboratory

The National Center for Biotechnology Information maintains the Genetic Testing Registry, an international database of genetic tests and genetic laboratories (www.ncbi.nlm.nih.gov/gtr).

ETHICAL CONSIDERATIONS OF GENETIC AND GENOMIC TESTING

Special considerations should be given to avoid presymptomatic testing in childhood for adult onset disorders for which no treatment is available. This practice is not recommended because of the psychological burden that such information poses for a child and his or her family, including guilt, blame, shame, denial, and survivor guilt among unaffected children. By testing children presymptomatically without offering treatment, at-risk children lose their autonomy including the right to decide for themselves whether and when they wish to be tested as adults. Presymptomatic testing also allows the possibility of future employment and insurance discrimination.

Genetic and genomic testing, such as the exome or genome sequencing trio test, may disclose sensitive information about family relationships including nonpaternity, conception with donated gametes, and adoption. It may reveal a disease state in a relative who is unprepared for such information. These possibilities reinforce the reasons that pretest informed consent is recommended for families of children undergoing genomic testing.

Even the hypothetical use of genome sequencing in healthy newborns as a possible technique for newborn screening raises concerns that should be examined carefully before implementing such a strategy, even in a limited way. Genetic information may have potentially damaging psychosocial effects within the family if it interferes with parent–child bonding or fosters the parent's perception of a child with a genetic variant as fragile or vulnerable (Frankel, Pereira, & McGuire, 2016). An individual's right to privacy and related concerns about access, storage, and security of genomic information and the chance of misuse of genetic information by corporate or government agencies must be weighed against the benefits to society that public health programs can deliver when they can efficiently and effectively screen and treat a population for preventable diseases.

RESOURCES ABOUT GENETIC DISORDERS FOR CLINICIANS AND FAMILIES

When a rare genetic diagnosis is made, treating providers need to become familiar with the disorder quickly and families need reliable resources. GeneReviews is a frequently updated and well-researched website that provides an excellent source of clinical information about specific genetic disorders (www.ncbi.nlm.nih.gov/books/NBK1116). The American Academy of Pediatrics has produced health supervision guidelines for achondroplasia, Down syndrome (trisomy 21), Fragile X syndrome, Marfan syndrome, neurofibromatosis type I, Prader–Willi syndrome, sickle cell disease, Turner syndrome, and Williams syndrome. They can be accessed by searching for "Health Supervision Guidelines" at https://aap.org. Information on many syndromes that is appropriate for families can be found at the Genetics Home Reference page, a site maintained by the National Institute of Health at https://ghr.nlm.nih.gov. The website maintained by the National Organization for Rare Disorders offers many resources for families and patients with genetic disorders in the United States at (https://rarediseases.org).

SUMMARY

Remarkable progress in the field of molecular genetics has improved the ability to diagnose critically ill newborns with neurobehavioral disorders, dysmorphic features, Mendelian disorder, intrauterine growth restriction, and congenital malformation syndromes. These advances bring with them the opportunity to diagnose more children at younger ages and improve medical care for a fragile and vulnerable population. However, genomic tests also have unique disadvantages and limitations. Some types of variants cannot be detected with NGS techniques. VUSs limit the utility of results. Families should receive informed consent about the unique aspects of genomic tests including their potential to reveal unsettling information about family relationships and predisposition for late-onset diseases. Our challenge as medical providers is to use these complex tools in the best interest of our patients by making informed and cost-effective choices. When we do our job well, the patient will receive the right test at the right time for the right reason.

ONLINE RESOURCES

Bull, M. J., Saal, H. M., Braddock, S. R., Enns, G. M., Gruen, J. R., Perrin, J. M., . . . Tarini, B. A. (2011). Clinical report—Health supervision for children with Down syndrome. *Pediatrics*, *128*(2), 393–406. doi:10.1542/peds.2011-1605

Genetic Testing Registry. Retrieved from https://www.ncbi.nlm.nih.gov/gtr

Online Mendelian Inheritance in Man. Retrieved from https://www.omim.org

Overview of the Human Genome Project. Retrieved from https://www.genome.gov/12011238/an-overview-of-the-human-genome-project

Talking Glossary of Genetic Terms. Retrieved from https://www.genome.gov/glossary

Understanding Rare Chromosomes and Gene Disorders. Retrieved from https://www.rarechromo.org

REFERENCES

Bachman, K. K., DeWard, S. J., Chrysostomou, C., Munoz, R., & Madan-Khetarpal, S. (2015). Array CGH as a first-tier test for neonates with congenital heart disease. *Cardiology in the Young, 25*(1), 115–122. doi:10.1017/S1047951113001868

Berg, J. S., Agrawal, P. B., Bailey, D. B., Jr., Beggs, A. H., Brenner, S. E., Brower, A. M., . . . Wise, A. L. (2017). Newborn sequencing in genomic medicine and public health. *Pediatrics, 139*(2), e20162252. doi:10.1542/peds.2016-2252

Bi, W., Borgan, C., Pursley, A. N., Hixon, P., Shaw, C. A., Bacino, C. A., . . . Cheung, S. W. (2013). Comparison of chromosome analysis and chromosomal microarray analysis: What is the value of chromosome analysis in today's genomic era? *Genetics in Medicine, 15*(6), 450–457. doi:10.1038/gim.2012.152

Boemer, F., Fasquelle, C., d'Otreppe, S., Josse, C., Dideberg, V., Segers, K., . . . Bours, V. (2017). A next-generation newborn screening pilot study: NGS on dried blood spots detects causal mutations in patients with inherited metabolic diseases. *Scientific Reports, 7*(1), 17641. doi:10.1038/s41598-017-18038-x

Borghesi, A., Mencarelli, M. A., Memo, L., Ferrero, G. B., Bartull, A., Genuardi, M., . . . Corsello, G. (2017). Intersociety policy statement on the use of whole-exome sequencing in the critically ill newborn infant. *Italian Journal of Pediatrics, 43*, 100. doi:10.1186/s13052-017-0418-0

Frankel, L. A., Pereira, S., & McGuire, A. L. (2016). Potential psychosocial risks of sequencing newborns. *Pediatrics, 137*(Suppl. 1), e20153731F. doi:10.1542/peds.2015-3731F

Geddes, G. C., Basel, D., Frommelt, P., Kinney, A., & Earing, M. (2017). Genetic testing protocol reduces costs and increases rate of genetic diagnosis in infants with congenital heart disease. *Pediatric Cardiology, 38*(7), 1465–1470. doi:10.1007/s00246-017-1685-7

Harris, S., Reed, D., & Vora, N. L. (2018). Screening for fetal chromosomal and subchromosomal disorders. *Seminars in Fetal and Neonatal Medicine, 23*(2), 85–93. doi:10.1016/j.siny.2017.10.006

Hayward, J., & Chitty, L. S. (2018). Beyond screening for chromosomal abnormalities: Advances in non-invasive diagnosis of single gene disorders and fetal exome sequencing. *Seminars in Fetal and Neonatal Medicine, 23*(2), 94–101. doi:10.1016/j.siny.2017.12.002

Lalani, S. E. (2017). Current genetic testing tools in neonatal medicine. *Pediatrics and Neonatology, 58*(2), 111–121. doi:10.1016/j.pedneo.2016.07.002

Malam, F., Hartley, T., Gillespie, M. K., Amour, C. M., Bariclak, E., Graham, G. E., . . . Dyment, D. A. (2017). Benchmarking outcomes in the neonatal intensive care unit: Cytogenetic and molecular diagnostic rates in a retrospective cohort. *American Journal of Medical Genetics, 173A*, 1839–1847. doi:10.1002/ajmg.a.38250

Meng, L., Pammi, M., Saronwala, A., Magoulas, P., Ghazi, A. R., Vetrini, F., . . . Lalani, S. R. (2017). Use of exome sequencing for infants in intensive care units: Ascertainment of severe single-gene disorders and effect on medical management. *JAMA Pediatrics, 171*(12), e173438. doi:10.1001/jamapediatrics.2017.3438

Ngo, T. T. M., Moufarrei, M. N., Rasmussen, M. H., Camunas-Soler, J., Pan, W., Okamoto, J., . . . Quake, S. R. (2018). Noninvasive blood tests for fetal development predict gestational age and preterm delivery. *Science, 360*(6393), 1133–1136. doi:10.1126/science.aar3819

Ombrone, D., Giocallere, E., Forni, G., Malvagia, S., & la Marca, G. (2016). Expanded newborn screening by mass spectrometry: New tests, future perspectives. *Mass Spectrometry Reviews, 35*(1), 71–84. doi:10.1002/mas.21463

Petrikin, J. E., Cakici, J. A., Clark, M. M., Willig, L. K., Sweeney, N. M., Farrow, E. G., . . . Kingsmore, S. F. (2018). The NSIGHT1-randomized trial: Rapid whole-genome sequencing for accelerated etiologic diagnosis in critically ill infants. *NPJ Genomic Medicine, 3*, 6. doi:10.1038/s41525-018-0045-8

Renga, B. (2018). Noninvasive prenatal diagnosis of fetal aneuploidy using cell free fetal DNA. *European Journal of Obstetrics, Gynecology, and Reproductive Biology, 225*, 5–8. doi:10.1016/j.ejogrb.2018.03.033

Ronan, A. (2018). Chromosome microarray analysis: A soothing guide. *Journal of Paediatrics and Child Health, 54*(6), 599–601. doi:10.1111/jpc.13869

Rosenfeld, M., Sontag, M. K., & Ren, C. L. (2016). Cystic fibrosis diagnosis and newborn screening. *Pediatric Clinics of North America, 63*(4), 599–615. doi:10.1016/j.pcl.2016.04.004

Shaffer, B. L., & Norton, M. E. (2018). Cell-free DNA screening for aneuploidy and microdeletion syndromes. *Obstetrics and Gynecology Clinics of North America, 45*(1), 13–26. doi:10.1016/j.ogc.2017.10.001

Therrell, B. B. L., Padilla, C. D., Loeber, J. G., Kneisser, I., Saadallah, A., Borrajo, G. J., & Adams, J. (2015). Current status of newborn screening worldwide: 2015. *Seminars in Perinatology, 39*(3), 171–187. doi:10.1053/j.semperi.2015.03.002

Toufaily, M. H., Westgate, M. N., Lin, A. E., & Holmes, L. B. (2018). Causes of congenital malformations. *Birth Defects Research, 110*(2), 87–91. doi:10.1002/bdr2.1105

CHAPTER 41

Trends in Neonatal Research and Evidence-Based Practice

Jana L. Pressler and Valerie Boebel Toly

INTRODUCTION

The focus of this chapter is on connecting neonatal nursing practice and research in such a way that the most valid and reliable knowledge available is translated into practice—known as best practice. The chapter presents knowledge on five distinct areas: (1) the basis of evidence-based practice (EBP), (2) models of evidence-based quality improvement, (3) clinical problems amenable to research, (4) various research-related roles for neonatal nurses, and (5) current trends in neonatal nursing research.

There is a growing call for nurses to lead quality improvement and transformation of healthcare through research and EBP. Experts point to the critical role that nurses have in leading interprofessional groups in producing safe, quality healthcare (Institute of Medicine [IOM], 2001, 2011). Conducting research and integrating results into clinical decision making are vital to this task.

Some type of knowledge and/or tradition guides every clinical decision and action taken by a nurse. The underlying rationale for a nursing intervention may be based on past experiences, trial and error, authority, a nursing procedure manual, textbook(s), or, most reliably, science produced through systematic inquiry (research). Nurses, along with most health professionals, have endorsed EBP as the knowledge foundation assuring the greatest likelihood that interventions will produce the intended outcome for the patient or the most accurate diagnosis of the condition. Progress, however, is sometimes held back by deeply rooted conventions in clinical decision making. In the past, nursing care policies often represented tradition ("we have always done it this way"), a source of knowledge known as "authority," the policy makers' own clinical experience, internal or external benchmarks, and information retrieved from textbooks. Moving from rationale grounded in tradition to EBP will increase the success of nursing care in assisting patients and families to better health.

Quality of care and resulting patient outcomes improve when interventions are selected based on research findings. Quality of care is defined as "the degree to which health care to individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge" (IOM, 2013). "That definition implies the nurse's application of cause-and-effect interventions known to be effective in resolving health issues." That definition also underscores key challenges in proceeding from research to evidence to practice. Specifically, there must be an available body of research-produced knowledge; intervention research needs to validate the likelihood that a given nursing intervention will produce the health outcome(s) desired; and care provided must align with what is known to be effective, as demonstrated through research in proceeding from research to practice.

THE BASIS OF EVIDENCE-BASED NEONATAL NURSING PRACTICE

Not all sources of knowledge are highly reliable nor does care based on various sources consistently produce the desired patient outcome. Experience and trial and error can be helpful; however, the knowledge gained through these approaches contains bias. That is, it is unknown whether results are due to the intervention or to something other than the intervention that is outside of the nurse's awareness. Additionally, results from one situation may not be generalizable (that is, applicable) to another situation or client for a variety of reasons. Clinical decisions drawn on experience and trial and error will not likely be the most effective in producing the patient outcome desired because these sources do not expose the entire truth or validity of broader reality. Also, knowledge resulting from trial and error (experience), not framed in explanatory models or theories, provides little to advance the scientific foundation for practice.

The underlying premise of EBP is that research studies produce the most valid and reliable source of knowledge on which to base clinical decisions. Today, the measure of "best practice" is that interventions are based on "best evidence," referring specifically to scientific findings. However, translating research into practice is fraught with obstacles. The work within the EBP paradigm itself has overcome a number of hurdles in applying research results in practice. EBP has established ways of applying research evidence in clinical decision making to ensure producing the best outcomes from scientific findings. Individual clinician decisions about care, as well as agency policies about care standards, should reflect the best evidence produced to date. The end result of applying state-of-the-science patient care is that healthcare status goals are effectively and efficiently met within the context of preferences of the patient, his/her family or significant others, and healthcare providers (Sackett, Straus, Richardson, Rosenberg, & Haynes, 2000). This rapidly advancing EBP movement comprises new methods and represents a new paradigm of research application in clinical care. The care environment in neonatal nursing exhibits many aspects of EBP whereby the entire neonatal healthcare team is engaged.

What Is EBP?

EBP is a process through which scientific evidence is identified, appraised, converted, and applied in healthcare interventions (Stevens, 2004). A widely accepted definition of EBP is that it is the integration of best research evidence, clinical expertise, and patient preference. The objective of EBP is the application of the best available evidence in clinical care in order to increase the likelihood that the desired patient outcome is achieved.

Although evidence and knowledge can be drawn from a variety of sources, the best evidence is specifically identified as evidence drawn from competently conducted (or robust) scientific investigation, or research (Guyatt, Rennie, Meade, & Cook, 2008). Using robust research evidence as the basis for care is best because it allows the nurse to gauge the certainty and predictability of the care in producing the intended outcome. Implementation of evidence into clinical decision making produces more accurate diagnosis, maximally effective and efficient intervention, and most favorable patient outcomes. These ends can be accomplished through EBP methods, processes, and models.

Using the keywords of "evidence-based practice" and "neonate," 119 publications were recently retrieved from Cumulative Index to Nursing and Allied Health Literature CINAHL) stemming from January 2010 to June 2018. These publications were grouped into nine broad categories (Table 41.1), beginning from most to fewest publications: infection ($n = 28$), caregiving ($n = 19$), feedings ($n = 15$), blood transfusions ($n = 14$), quality of care ($n = 12$), respiratory related ($n = 11$), drug studies ($n = 10$), birth experience ($n = 6$), and safety related ($n = 4$). Knowledge gleaned from these publications could comprise a succinct neonatal textbook in and of itself.

Because EBP findings might not be generalizable outside of the context or location of where studies were conducted, the publications were categorized by geographic origin of the publication. U.S. authors had the most (62) and Australia/New Zealand had the second most (15) publications. The origin of the other publications were broken down as follows: Europe (13), the United Kingdom (UK; 12), Asia (8), Canada (6), South America (2), and Africa (1). Two unexpected findings in completing this CINAHL search were that there were not more EBP publications emanating from Canada

TABLE 41.1

EBP PUBLICATIONS, JANUARY 2010 THROUGH JUNE 2018 IN ORDER OF PUBLICATION BY TOPIC

First Author	EBP Topic	Geographic Region
Infections (n = 28)		
Patel, S. V.	Presence of infections	UK
Manley, D.	Wound therapy	United States
Sharpe, E.	Central line care	United States
Ares, G.	Central line	United States
Khalifian, S.	Skin care practices	United States
Esser, M.	Wound therapy	United States
Jollett, E.	Preventing necrotizing enterocolitis	United States
Stewart, D.	Umbilical cord care practices	United States
Grosvenor, J.	Skin care practices to prevent skin injury	UK
Weber, C. D.	Preventing ventilator-associated pneumonia	United States
Lefrak, L.	Preventing infections due to vascular access	United States
Higgins, R. D.	Preventing infections secondary to chorioamnionitis	United States
Zhou, Q.	Multifaceted central line infection prevention	Asia
Kurz, E.	Culture-based screening for prevention of group B streptococcus	Australia
Balkhy, H. H.	Infection control using a multimodal bundle strategy	Asia

(*continued*)

TABLE 41.1

EBP PUBLICATIONS, JANUARY 2010 THROUGH JUNE 2018 IN ORDER OF PUBLICATION BY TOPIC (*continued*)

First Author	EBP Topic	Geographic Region
Homer, C. S. E.	Screening for the prevention of group B streptococcus	Australia
Taylor, J. E.	Varied effectiveness of central venous catheter care	Australia
Zhou, Q.	Multifaceted care reducing pneumonia	Asia
Folgori, L.	Hospital-acquired bloodstream infections in NICUs	UK
Krowchuk, H.	Baby wash product effectiveness as a skin barrier	United States
Elser, H. E.	Basic bathing practices for newborns	United States
Hocevar, S. N.	Infection control to prevent MRSA and CLABSI	United States
Krowchuk, H. V.	Heparinized versus normal saline for IV maintenance	United States
Agrawal, P. K.	Clean cord cutting practices in India	Asia
Williams, N.	Use of barrier-enhancing emollient in preterm infants	UK
Huskins, W. C.	Quality improvement to prevent CLABSI infections	United States
Manzoni, P.	Three preventive strategies for three types of sepsis	Europe
Sannoh, S.	Multimodal central venous catheter care and infection	United States
Caregiving Related (n = 19)		
Kam, M.	Multifaceted training and intravenous extravasation	Asia
Da Silveira Magalhães, S.	Care of infants with congenital heart disease	South America
Luton, A.	Skin protection to prevent pressure injuries	United States
Young, E. E.	Improving pain management for neonates	United States
Racine, E.	Five principles for caring for neurologic injuries	Canada
Disher, T.	Skin-to-skin contact	Canada
Ali, S.	Pain management in the ER	Canada
Bowman, D. S.	Thermoregulation	United States
Lee Wan Fei, S.	Positioning and phototherapy hyperbilirubinemia	Asia
da Motta, P.	Pain management	South America
Khoza, S. L. T.	Pain management	Africa
Kennard, P. G.	Thermoregulation	United States

(*continued*)

TABLE 41.1

EBP PUBLICATIONS, JANUARY 2010 THROUGH JUNE 2018 IN ORDER OF PUBLICATION BY TOPIC (*continued*)

First Author	EBP Topic	Geographic Region
Burke, L.	Appropriate thermoregulation	United States
Smith, J.	Temperature measurement	Australia
Smith, J.	Temperature measurement	Australia
Hellowell, F.	Hyperbilirubinemia care	UK
Stapelkamp, C.	Assessment of acute pain	UK
Losacco, V.	Heel blood sampling in European NICUs—pain management	Europe
Mokhnach, L.	Management of neonatal procedural pain	United States
Feeding Related (n = 15)		
Lee, S.	Feedings and tracheal esophageal fistula	United States
Agrawal, S.	Iron intake	United States
Goldfield, E. C.	Feeding behavior	United States
Capilouto, G. J.	Feeding behavior	United States
Whetten, C. H.	Feeding behavior	United States
Stricklin, M.	Skin-to-skin care in the OR to increase breastfeeding	United States
Clifford, P.	Enteral tube placement	United States
Athalye-Jape, G.	Food supplements	Australia
Parker, R.	Probiotic guideline for necrotizing enterocolitis	United States
Csont, G. L.	Breastfeeding neonates	United States
Srinivasjois, R.	Prebiotic supplementation	Australia
Pletsch, D.	Early colostrum use	Canada
Goulet, O.	Neonatal short bowel syndrome and enteral feeding	Europe
Deshpande, G. C.	Probiotics in preterm neonates	United States
Onwuneme, C.	Vitamin D supplementation	UK
Blood Transfusions (n = 14)		
Türkmen, T.	Blood transfusion care	Europe
Borja, C.	Umbilical cord clamping	United States

(*continued*)

TABLE 41.1

EBP PUBLICATIONS, JANUARY 2010 THROUGH JUNE 2018 IN ORDER OF PUBLICATION BY TOPIC (*continued*)

First Author	EBP Topic	Geographic Region
Patel, R. M.	Blood transfusion care	United States
Keir, A. K.	Blood transfusion care	Australia
Sola-Visner, M.	Blood transfusion care	United States
Del Vecchio, A.	Blood transfusion care	Europe
Ullman, A. J.	Anemia and blood sampling	Australia
Beniwal, L.	Quality improvement outcomes with blood transfusion	United States
Nickel, R. S.	Blood transfusion care	United States
Motta, M.	Blood transfusion care	Europe
Renzaho, A. M. N.	Blood transfusion care	Australia
Christensen, R. D.	Blood transfusion care	United States
Christensen, R. D.	Blood transfusion care	United States
Del Vecchio, A.	Transfusion recommendations	Europe
Quality of Care (n = 12)		
Wells, S.	Quality of care—New Zealand or UK	New Zealand/UK
Álvarez, M. J.	Massage therapy	Europe
Kain, V. J.	Palliative care	Australia
Quinn, M.	Palliative care	United States
Altimier, L.	Developmental care	United States
Watson, T. A.	Rounding to enhance communication with parents	United States
Trembath, A. N.	Quality initiatives	United States
Lawrence, C.	Interdisciplinary plans of care	United States
Kong, L-P.	Anxiety and depression in parents	Asia
Byrne, E.	Physical therapy observations	United States
Placencia, F. X.	Parental care for neonates, parental counseling	United States
Hignett, S.	Treatment space in neonatal cot spaces	UK

(*continued*)

TABLE 41.1

EBP PUBLICATIONS, JANUARY 2010 THROUGH JUNE 2018 IN ORDER OF PUBLICATION BY TOPIC (*continued*)

First Author	EBP Topic	Geographic Region
Respiratory Related (n = 11)		
Hughes Driscoll, C. A.	Nitric oxide	United States
Sweet, M.	Safe suctioning	United States
Casey, J. L.	Early bubble CPAP	United States
Motojima, Y.	High-flow nasal cannula	Asia
Martin, S.	Bubble CPAP safety in low-income countries	Australia
Kurland, G.	Interstitial lung disease	United States
Gowda, H.	Placement of endotracheal tubes	UK
DiBlasi, R. M.	Inhaled nitric oxide for hypoxic respiratory failure	United States
Robertson-Malt, S.	Intra-amniotic surfactant and preterm infants	Australia
Gale, C.	Capillary refill time and circulatory status	UK
Kalyn, A.	Suctioning the intubated neonate	United States
Drug Related (n = 10)		
Elie, V.	Drug study	Europe
Krans, E. E.	Opioid use	United States
Teague, A.	Intraprofessional excellence neonatal abstinence	United States
Leroux, S.	Prescribing antibiotics	Europe
Cramton, R. E. M.	Neonatal and iatrogenic withdrawal syndromes	United States
Sammons, H. M.	Vancomycin use	UK
Johnston, P. G.	Use of indomethacin and ibuprofen	United States
Noori, S.	Blood pressure support using vasopressor agents	United States
Monagle, P.	Antithrombotic therapy and thrombosis prevention	Australia
Shah, P. S.	Propofol for procedural pain	Canada
Birth Experience (n = 6)		
Schwartz, S.	Transport	United States
Edmondson, M.	Water birth	UK

(*continued*)

TABLE 41.1

EBP PUBLICATIONS, JANUARY 2010 THROUGH JUNE 2018 IN ORDER OF PUBLICATION BY TOPIC (*continued*)

First Author	EBP Topic	Geographic Region
Khriesat, W.	Newborn resuscitation	Europe
Kukora, S.	Limit of viability	United States
Schmölzer, G. M.	Ventilation at birth during resuscitations	Canada
Nutter, E.	Water birth	United States
Safety Related (n = 4)		
Sonnemans, L. J. P.	Postmortem radiology for determining diagnosis	Europe
Santesteban, E.	Medication errors and ways to prevent them	Europe
Krowchuk, H.	Infant car seats	United States
Beall, V.	Neonatal extravasation due to IV infiltration	United States

CLABSI, central line–associated bloodstream infections; CPAP, continuous positive airway pressure; EBP, evidence-based practice; ER, emergency room; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; NICU, neonatal intensive care unit; OR, operating room; UK, United Kingdom

and Asia, where research appears to be heavily pursued and highly regarded, and the fact that there were quite a few published EBP articles involving neonatal blood transfusions. Only one publication was focused on EBP for developmental care of neonates.

As is summarized in Table 41.2, some geographic areas originated very few EBP publications over the past 8 years. Thus, caution must be used when considering EBP findings from other geographic areas and when planning care using EBP findings in these less published geographic areas. It is especially important to consider individual provider and organizational factors that influence the adoption of practice evidence when the evidence was generated in very different healthcare environments or contexts. It might not be effective, for example, to apply practice guidelines that were developed in the United States to neonatal units in South America or Africa because psychosocial and healthcare delivery systems vary in such a way that knowledge is not generalizable.

MODELS OF EVIDENCE-BASED QUALITY IMPROVEMENT

Evidence-based nursing practice is the process of establishing research-based practice (RBP) by transforming research knowledge into practice and patient outcomes. Over 14 years ago, nurse scientists developed the ACE five-point Star Model of Knowledge Transformation to explain the conversion necessary to enhance the clinical utility of research results by reducing the volume and complexity of research knowledge, converting one form of knowledge to the next, and incorporating a broad range of sources of knowledge throughout the EBP process (Stevens, 2004). Stevens's five-point Star Model provides a framework for considering the transformation that takes place from a single research report in a form with low clinical utility (e.g., statistical test results in a primary research report) into a form that has high utility in clinical decision making and that is firmly integrated into clinical practice. Knowledge transformation through five related forms is depicted as a five-point process (Figure 41.1). The forms of knowledge in this transformation are (a) primary research, (b) evidence summary, (c) translation, (d) integration, and (e) evaluation (Stevens, 2004, 2012; Stevens, Pepper, Horn, & Mitchell, 2017). Each form moves progressively forward in its usefulness for clinical decisions at the point of care, ending with measuring the impact of the evidence-based improvement.

Point One of Stevens's Star Model is represented by single, primary research studies. This is the knowledge form with which nurses are most familiar—individual reports of research studies. Over the past 50 years, nurse researchers have conducted thousands of research studies on a wide variety of nursing clinical topics. Although primary research is requisite to EBP, such research does not hold a great deal of stable, accessible usefulness in clinical decision making. The body of primary research on any given topic will likely include both a variety of study designs, small and large samples, and conflicting or converging results, leaving clinicians uncertain about which studies are the best reflection of cause and effect in selecting effective interventions. In addition, the body of research on a given clinical topic might include hundreds of studies and, as such, not be useful for clinical decision making. In considering the form of knowledge on Star Point One for clinical decision making, two major challenges exist: (1) volume and (2) complexity of research literature.

In **Point Two of Stevens's Star Model**, single research studies are transformed into clinically useful knowledge using an evidence summary approach. In this second stage of knowledge transformation, all primary research on a given clinical topic is systematically gathered, screened, and summarized into a single statement about the state of knowledge on the topic. This summary step is considered the key step for moving research into practice (Eden, Wheatley, McNeil, & Sox, 2008). Systematic reviews (SRs) transform research knowledge in numerous ways and offer advantages, as summarized in Box 41.1. Evidence summaries present the latest

TABLE 41.2

GEOGRAPHIC REGION WHERE PUBLICATIONS ORIGINATED, JANUARY 2010 THROUGH JUNE 2018

	Geographic Origin								
Broad Area of EBP	**United States**	**Australia/NZ**	**Europe**	**UK**	**Asia**	**Canada**	**South America**	**Africa**	**Total**
Infections	16	3	1	4	4	0	0	0	**28**
Caregiving related	6	2	1	2	2	3	2	1	**19**
Feeding related	10	2	1	1	0	1	0	0	**15**
Blood transfusions	7	3	4	0	0	0	0	0	**14**
Quality of care	7	2	1	1	1	0	0	0	**12**
Respiratory related	6	2	0	2	1	0	0	0	**11**
Drug related	5	1	2	1	0	1	0	0	**10**
Birth experience	3	0	1	1	0	1	0	0	**6**
Safety related	2	0	2	0	0	0	0	0	**4**
TOTALS	**62**	**15**	**13**	**12**	**8**	**6**	**2**	**1**	**119**

EBP, evidence-based practice; NZ, New Zealand, UK, United Kingdom

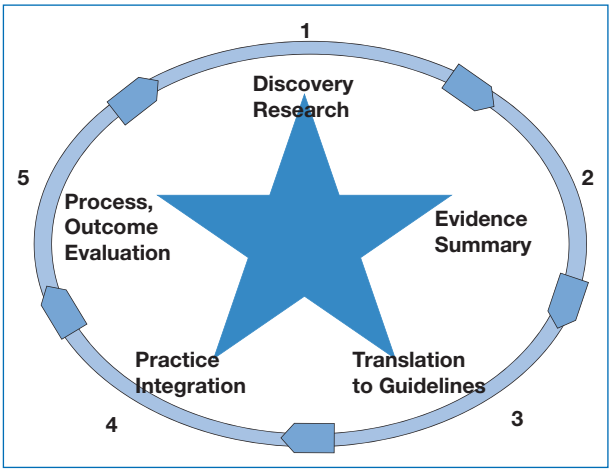

FIGURE 41.1 Stevens Star Model of Knowledge Transformation.

Source: Copyright © Stevens, K. R. (2015). *Star Model of EBP: Knowledge transformation.* Academic Center for Evidence-based Practice, San Antonio: The University of Texas Health Science Center at San Antonio.. Reprinted with expressed permission.

Box 41.1

ADVANTAGES OF SYSTEMATIC REVIEWS

A systematic review accomplishes the following:

Reduces large quantities of information to a manageable form

Integrates existing information for decisions about clinical care, economic decisions, future research design, and policy formation

Increases efficiency in time between research and clinical implementation

Establishes generalizability across participants, settings, treatment variations, and different study designs

Assesses consistency and explains inconsistencies of relationships across studies

Increases power in suggesting cause-and-effect relationship(s)

Reduces bias from random and systematic error, improving true reflection of reality

Provides better continuous updates of new evidence

SR, systematic reviews.

Source: Adapted from Mulrow, C. (1994). Rationale for systematic reviews. *British Medical Journal, 309*, 597–599. doi:10.1136/bmj.309.6954.597

scientific findings in an accessible form, both for the clinical nurse to readily apply in clinical decisions and to also create clinical unit policies. When developing an evidence summary, reviewers must keep in mind that nonsignificant findings can be as important to practice as statistically significant findings. However, nonsignificant findings tend not to be regarded as worthy of publication and, subsequently, are underrepresented in the literature.

Evidence summaries are developed by various groups and referred to using several terms: evidence synthesis, SRs, and integrative reviews. The most widely used methods in rigorous evidence summaries produce a SR that reflects the SR methods established in the mid-1990s (Higgins & Green, 2011). A SR is a type of evidence summary that uses a rigorous scientific approach to combine results from a body of primary research studies into a clinically meaningful whole. SR involves a research design that produces new knowledge through synthesis. SR typically uses the statistical procedure of meta-analysis to combine findings across multiple studies. Meta-analysis removes voluminous and rapidly expanding bodies of literature from the findings. SRs are rated as the strongest evidence for best practice. In addition, if summaries are not systematically developed, there is a risk of drawing erroneous conclusions about whether or not an intervention actually works. If this is the case, nurses may select interventions that do not work as intended, or be unaware of interventions that do work as intended.

Developing sound evidence summaries requires time—often over a year's worth of scientific teamwork, specialized scientific skill, and extensive resources. If an evidence summary is completed to meet rigorous standards, evidence summaries will

- Include research that has been reviewed from all relevant disciplines and across the globe
- Screen studies for quality of design and relevance
- Use multiple reviewers to abstract the findings
- Analyze the results to combine findings and examine extent of bias in the set of research studies

Therefore, evidence summaries are often conducted by scientific and clinical teams who are specifically prepared in evidence summary methodology.

Point Three of Stevens's Star Model occurs through translation of resulting knowledge once an evidence summary is conducted. In this stage, content experts are called upon to review the evidence summary, fill in gaps with consensus expert opinion, and merge research knowledge with expertise to produce clinical practice guidelines (CPGs). This translation process converts the research evidence into clinical recommendations.

New standards for developing CPGs specify processes that will produce high-quality, trustworthy guidelines, assuring that recommendations reflect current knowledge. A number of clinical specialty organizations produce these types of clinical guidelines. For example, the Association of Women's Health, Obstetric, and Neonatal Nurses (AWHONN) developed an excellent example of a CPG for late preterm infants (AWHONN, 2010). The association combined research evidence and clinical expertise to produce evidence-based guidelines on assessment and care of the late preterm infant. This was achieved by (a) locating and explicating the evidence, (b) rating the strengths of evidence (including evidence-based recommendations), and (c) publishing the guideline.

Trustworthy CPGs reflect several characteristics:

1. A specified process is followed during guideline development.
2. The guideline identifies the evidence on which each recommendation is based, that is, specifically whether it is research or expert opinion.
3. The evidence is rated using a strength-of-evidence rating scale (Graham, Mancher, Wolman, Greenfield, & Steinberg, 2011).

Once such guidelines are produced, integration is accomplished through change at both the individual clinician and the organizational levels. Other, less rigorously developed guidelines are present throughout healthcare in the form of **clinical pathways, nursing care standards, and unit policies**. However, because they are believed to be more valid and reliable, CPGs should be used as the guidelines of choice to the extent that it is feasible.

Point Four of Stevens's Star Model encompasses integration of a CPG into practice at individual provider, microsystem, and system levels. Planned change approaches often are used to overcome

resistance and move the individual and organization to a higher standard of practice based on evidence. Guidance for planned change is provided by principles and theories. For example, first, because quality is a system property, systems must be changed with EBP; and second, adoption of new practices can be amplified using principles from theories—such as Rogers's theory of diffusion of innovation (Rogers, 1995). As advances unfold in neonatal nursing, it is essential that all members of the healthcare team be actively involved in making quality improvement changes in caregiving. Nurses will serve as leaders and followers in contributing to such improvements at the individual as well as the system level of care.

Point Five of Stevens's Star Model is evaluation. Practice changes are followed by evaluation of the impact on various outcomes, including effectiveness of the care in producing desired patient outcome; population outcomes; efficiency and cost factors in the care (short and long term); and satisfaction of providers' and patients' families. Evaluation of specific outcomes has risen to a high level of public interest, given people's awareness that American healthcare might neither be safe nor effective (Kohn, Corrigan, & Donaldson, 2000). As a result, quality indicators have been established for healthcare improvement and for public reporting (e.g., Agency for Healthcare Research and Quality [AHRQ], 2012a, 2012b).

Major Features of EBP

Barriers to implementing EBP are removed by using evidence syntheses as the basis for clinical recommendations. SRs "efficiently integrate valid information and provide a basis for rational decision-making" in clinical care (Mulrow, 1994). Only in rare instances will a single research study offer highly reliable answers to a clinical question (Eden, Levit, Berg, & Morton, 2011). It is most feasible for nurses to use research evidence that has been summarized in the form of a SR. Because conducting evidence syntheses is a new, resource-intensive, labor-intensive, and rigorous process, it is beyond the capacity of and time allotted to most clinicians in their daily routine. For those reasons alone, it is critical that clinicians be aware of existing sources of synthesized evidence. Box 41.2 presents examples of evidence summaries from the *Cochrane Library of Systematic Reviews*. In addition, Table 41.3 describes other credible sources for evidence summaries. In some cases, conclusions from the evidence summary support current practice and increase confidence that nursing care will produce the desired outcome. In other cases, the evidence points to a needed change in practice. In either case, examining current practice in light of the state of the science is becoming expected in healthcare.

Sources of Evidence for Nursing Practice

Recognizing that considerable work needs to be done to translate research into practice, a number of entities are adding to the collection of forms of knowledge available to clinicians. These EBP points are now populated by several resources, guiding nurses to useful forms of knowledge for clinical decision making. Synthesis work is conducted by several organized agencies. Because the conduct of a SR requires specialized scientific methods and significant resources, it is usually a sponsored work activity spurred by influential agencies such as the IOM and AHRQ. Each point of Stevens's Star Model is conducted by groups of scientists. The leading agencies pursuing this work are the Cochrane Collaboration (a global collaborative headquartered in the United Kingdom) and the AHRQ (a federally funded agency in the United States). Another source of evidence summaries is the Joanna Briggs Institute (JBI), headquartered in Adelaide, South Australia. The JBI has centers for EBP and conducts SRs around the world. In turn, these agencies disseminate the evidence summaries for use by clinicians, health policy makers, and consumers of healthcare (Table 41.3).

Point Three of Stevens's Star Model is populated by several agencies that develop or provide large collections of CPGs. The AHRQ supports the National Guidelines Clearinghouse, a searchable collection of almost 2,000 CPGs, most with strong evidential

Box 41.2

EXAMPLES OF EVIDENCE SUMMARIES OR PROTOCOLS ON NEONATAL NURSING CARE IN THE COCHRANE DATABASE OF SYSTEMATIC REVIEWS

Bell, E. F., & Acarregui, M. J. (2014). Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants. *Cochrane Database of Systematic Reviews*, (12), CD000503. doi:10.1002/14651858.CD000503.pub3

Collins, C. T., Gillis, J., McPhee, A. J., Suganuma, H., & Makrides, M. (2016). Avoidance of bottles during the establishment of breast feeds in preterm infants. *Cochrane Database of Systematic Reviews*, (10), CD005252. doi:10.1002/14651858.CD005252.pub4

Conde-Agudelo, A., & Diaz-Rossello, J. L. (2016). Kangaroo mother care to reduce morbidity and mortality in low birthweight infants. *Cochrane Database of Systematic Reviews*, (8), CD002771. doi:10.1002/14651858.CD002771.pub4

Foster, J. P., Psaila, K., & Patterson, T. (2016). Non-nutritive sucking for increasing physiologic stability and nutrition in preterm infants. *Cochrane Database of Systematic Reviews*, (10), CD001071. doi:10.1002/14651858.CD001071.pub3

Johnston, C., Campbell-Yeo, M., Disher, T., Benoit, B., Fernandes, A., Streiner, D., . . . Zee, R. (2017). Skin-to-skin care for procedural pain in neonates. *Cochrane Database Systematic Review*, (2), CD008435. doi:10.1002/14651858.CD008435.pub3

Morag, I., & Ohlsson, A. (2016). Cycled light in the intensive care unit for preterm and low birth weight infants. *Cochrane Database Systematic Review*, (8), CD006982. doi:10.1002/14651858.CD006982.pub4

Rivas-Fernandez, M., Roque I Figuls, M., Diez-Izquierdo, A., Escribano, J., & Balaguer, A. (2016). Infant position in neonates receiving mechanical ventilation. *Cochrane Database of Systematic Reviews*, (11), CD003668. doi:10.1002/14651858.CD003668.pub4

Spittle, A., Orton, J., Anderson, P. J., Boyd, R., & Doyle, L. W. (2015). Early developmental intervention programmes provided post hospital discharge to prevent motor and cognitive impairment in preterm infants. *Cochrane Database of Systematic Reviews, (11),* CD005495. doi:10.1002/14651858.CD005495.pub4

Stevens, B., Yamada, J., Ohlsson, A., Haliburton, S., & Shorkey, A. (2016). Sucrose for analgesia in newborn infants undergoing painful procedure. *Cochrane Database of Systematic Reviews*, (7), CD001069. doi:10.1002/14651858.CD001069.pub5

Weston, P. J., Harris, D. L., Battin, M., Brown, J., Hegarty, J. E., & Harding, J. E. (2016). Oral dextrose gel for the treatment of hypoglycaemia in newborn infants. *Cochrane Database of Systematic Reviews*, (5), CD011027. doi:10.1002/14651858.CD011027.pub2

TABLE 41.3

ALPHABETICAL LIST OF SOURCES OF SYSTEMATIC REVIEWS ON THE INTERNET

Systematic Review Source	Address
Agency for Healthcare Research and Quality	www.ahrq.gov
Cochrane Collaboration	https://us.cochrane.org/ (introductory information)
Joanna Briggs Institute	https://joannabriggs.org/
Sigma Theta Tau International's Worldviews on Evidence-Based Nursing	http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1741-6787
U.S. Preventive Services Task Force	www.ahrq.gov/clinic/uspstfix.htm

Source: Adapted from Stevens, K. R., & Pugh, J. A. (1999). Evidence-based practice and perioperative nursing. *Seminars in Perioperative Nursing, 8*(3), 155–159.

TABLE 41.4

THE FIVE POINTS OF THE STAR MODEL AND SAMPLE COMPETENCIES FOR NURSES

Star Point	Competency
1. Original research	Recognize ratings of strength of evidence when reading literature including web resources
2. Evidence summary	List advantages of SRs as strong evidential foundation for clinical decision making
3. Translation	Use specified databases, access CPGs on various clinical topics
4. Integration	Assist in integrating practice change based on EB CPGs
5. Evaluation	Participate in EB quality improvement processes to evaluate outcomes of practice changes

CPG, clinical practice guidelines; EB, evidence-based; SR, systematic review.

Source: Adapted from Stevens, K. R. (2009). *Essential competencies for evidence-based practice in nursing.* San Antonio: University of Texas Health Science Center. Reprinted with permission from Kathleen R. Stevens, RN, EdD, ANEF, FAAN; UT Health Science Center.

foundations. In the United Kingdom, the National Institute for Health and Clinical Excellence (NICE; www.nice.org.uk) develops evidence-based guidelines for healthcare providers, as well as for patients and caregivers. There is growing interest in promoting global collaboration in the development and evaluation of EBP guidelines. One organization that has formed to promote such collaboration is the Guidelines International Network, with members from 46 countries and an international guidelines library that contains more than 7,400 documents (Guidelines International Network, 2012). Another excellent resource for evidence-based neonatal care is the Vermont Oxford Network that was established in 1988 and now includes 9,000 neonatal units worldwide. Member institutions participate in research and also have the option of participating in a quality improvement neonatology collaborative to identify and implement best practices in neonatal care (Vermont Oxford Network, 2012).

Point Four of Stevens's Star Model is now populated by the AHRQ Healthcare Innovations Exchange, with the goal of speeding integration of new and better ways of delivering and improving quality of healthcare. Almost 600 innovations are profiled, along with adopter's guidelines and tools for adopting and sustaining the innovation. Additionally, Point Five, evaluation, is populated by a number of initiatives to measure and track the quality and safety of care. Quality indicator initiatives include the AHRQ National Healthcare Quality and Disparities Reports and National Database of Nursing Quality Indicators. System-level indicators include surveys of the agency's culture of patient safety and attainment of "never" events.

Essential Skills in Using EBP

The skills required to accomplish EBP range from the frontline clinician's openness to credible changes in practice to the statistician performing meta-analysis. At each clinician level and discipline, there are crucial competencies needed in terms of skills, attitudes, and actions. Although the principles and goals of EBP are readily apparent, the paradigm requires a shift in the way that nurses have traditionally perceived research and clinical decision making. Through an iterative process with an expert panel, national consensus about essential competencies for EBP in nursing has been established (Stevens, 2009). Table 41.4 provides examples of these competencies for the staff nurse level, organized by the five points contained on the Star Model. The competencies are organized across three levels of clinical practice: (1) entry (staff nurse), (2) intermediate (e.g., CNS or midlevel manager), and (3) advanced (e.g., doctoral nurse participating in a SR team). In addition, the competencies span the five points of the Star Model.

How to Integrate EBP in Nursing Practice?

With the new insights into effective clinical decision making that EBP has provided, the question becomes "How is EBP employed?" Although a number of methods are being developed, tested, and adopted, several guiding principles are apparent. In today's trends, adoption of EBP is connected to clinical effectiveness and patient safety. EBP is connected to the agency's goal of improving care and outcomes. In clinical settings, often the administrative and managerial teams come to a conclusion that the agency will adopt an initiative: to employ EBP throughout their healthcare. The commitment requires time, leadership, engagement across all stakeholders, and resources; so, several planning stages help make the initiative a success. These planning stages are as follows:

1. The plan for employing EBP may initially include announcements, persuasion for buy-in from all vested interests, and identification and mobilization of resources. Of the many resources needed, *time* in the clinician's workday is a key resource. Other resources can be drawn from existing departments such as the quality assurance department, the medical librarian, and academicians from collaborating universities.
2. To focus the EBP effort, clinical priority topics are identified and set out as the first targets for evidence-based quality

improvement. To be successful, the organization and healthcare team are involved. Criteria useful for selecting priority topics are those established by the IOM to identify national priorities for healthcare improvement (Adams & Corrigan, 2003). These are (a) *impact* in terms of burden on patient, family, healthcare system, and society; (b) evidence that already exists for *improvability* but is not yet used in standard care; and (c) *inclusiveness*, reflecting applicability to patients across the life span and settings.

3. Evidence is located. A comprehensive search is essential, and professional information management skills are valuable. Beginning with a search for evidence summaries is often productive in locating reviews that have already been completed. Locating other forms of knowledge, such as primary research and CPGs, is also important in this step.
4. Critical appraisal of the evidence can be accomplished by an evidence team. Using existing checklists, the validity and strength of the evidence are rated.
5. An evidence-based CPG is adapted from an existing one or developed by the team. This CPG development process should be standardized to ensure that evidence is explicated and rated in all CPGs that are introduced into practice.
6. Quality indicators are selected, and baseline assessments are made.
7. A comprehensive plan for change, adoption of innovation, and integration into practice is developed and implemented.
8. The targeted quality indicators are measured again and then compared to baseline assessment. These outcome measures should include patient outcomes, health status (population) indicators, and cost impact. The impact on the care process is also measured to determine if clinical practice has been true to the prescribed CPG. Feedback from quality audits is effective in stabilizing the change to the new standard of care.

Global Considerations to Be Made in Using EBP

Implementing EBP may be challenging to nurses who live in low-resource countries that have limited access to the Internet and thus have limited opportunities to review the literature or identify evidence to guide practice. One resource that can help to improve access to information resources is the eGranary database of digital resources (www.widernet.org/eGranary). eGranary was founded in 2001 to provide access to Internet resources for the estimated seven out of eight people worldwide with limited Internet access. With support from numerous partner institutions and volunteers, digital and web-based resources are copied onto the eGranary server (after securing copyright permission), and these resources are then available to those who purchase the reasonably priced server. As an example of the capability of eGranary to disseminate knowledge, the University of Alabama at Birmingham Sparkman Center for Global Health has worked with numerous partners to develop a portal of more than 500 resources. This portal supports evidence-based nursing practice in Zambia and other English-speaking countries (eGranary Digital Library, 2012).

Another resource to improve access to evidence for nurses in low-resource countries who have Internet access is the Health Internet Access to Research Initiative (HINARI) Access to Research for Health Programme, set up by the World Health Organization (WHO) together with major publishers. HINARI enables developing countries to gain access to one of the world's largest collections of biomedical and health literature. It provides free or low-cost Internet access to more than 8,000 journals and online resources to not-for-profit institutions in low-resource countries (HINARI Access to Research for Health Programme, n.d.).

CLINICAL PROBLEMS AMENABLE TO RESEARCH

Neonatal nurses can use findings from research as well as other evidence to improve and change neonatal nursing practice. As previously noted, the first step in developing an EBP protocol or procedure is the identification of a clinical problem to be addressed.

Nurses might start by identifying a problem of concern in their individual clinical setting. Nurses in the clinical setting are often in the best position to identify and articulate highly relevant research questions and, through partnering with scientists, are able to carry out research studies that directly improve the delivery of nursing care. The types of questions posed by clinical nurses range from basic physiologic mechanisms in neonatal health to comparisons of efficacy between various interventions to identification of new phenomena as the topic for new programs of research. Ideas for research come from many different sources, including an individual nurse's experience, the nursing or health literature, discussions of social or health issues, or theory (Burns & Grove, 2009). With today's increased emphasis on quality and safety, research topics also emerge from quality assurance audits in the clinical unit, agency-wide interest in system support for quality and safety, and national recommendations for healthcare delivery changes.

Researchers and professional organizations sometimes conduct surveys or convene expert panels to identify research priorities. These priorities can also help researchers identify researchable problems. For example, the Strategic Plan for the National Institute of Nursing Research (NINR) identified four areas that will be the focus of research investment between 2016 and 2021: (a) symptom science: promoting personalized health strategies; (b) wellness: promoting health and preventing disease; (c) self-management: improving quality of life for individuals with chronic illness; and (d) end-of-life and palliative care: the science of compassion. In addition, the NINR included two crosscutting topics vital to the advancement of nursing science: (a) promoting innovation: technology to improve health; and (b) 21st century nurse scientists: innovative strategies for research careers (NINR, 2016). NINR promotes interdisciplinary research using a variety of methods including intervention studies, translational research programs, and research to evaluate costs, outcomes, and quality of care (NINR, 2011). In parallel, the Improvement Science Research Network (ISRN) established research priorities in improving healthcare delivery that works in tandem with the NINR clinical research topics (ISRN, 2010). The ISRN research priorities underscore a new goal for nursing research, that is, to discover which improvement interventions are effective in changing healthcare delivery. The broadly stated ISRN research priorities include (a) transitions and coordination in care across healthcare delivery segments; (b) high-performing clinical systems and microsystems; (c) evidence-based quality improvement and best practices; and (d) learning organizations and culture of quality and patient safety (ISRN, 2010).

Box 41.3 lists topics of current research interest questions for neonatal nurses. Many of these research questions are derived from the concern about the prevention of iatrogenic complications of treatments. Others emerge from systematic observation of clinical phenomena or from frustration with current practices.

The Role of Neonatal Nursing Organizations

Neonatal nursing organizations also assist with the identification of neonatal research priorities and development of EBP guidelines. For example, in 1990, the AWHONN convened a panel of nurse experts to identify areas with sufficient research to develop

Box 41.3

SOME CURRENT NEONATAL NURSING RESEARCH QUESTIONS

Skin Care

How can epidermal damage from tape removal be reduced?

Can the permeable skin of preterm infants be used to deliver medication?

How can the barrier properties of the skin be improved to prevent infection and water loss?

Which cleansing agent and bathing techniques are best for preterm and full-term infants?

Do emollients prevent transepidermal water loss and dermatitis in premature infants?

What is the reliability and validity of the neonatal skin condition score?

Nutrition

How can breastfeeding practices be promoted among mothers of premature infants?

What are the most effective methods of feeding preterm infants?

What are the effects of kangaroo care on breast milk production?

What is the relationship between preterm infant behavioral states and feeding efficiency?

What is the effect of side-lying position on oral feeding outcomes in preterm infants?

What are the supports and barriers to the provision of human milk by mothers of preterm infants?

Instruments and Procedures

What is the effect of routine care tasks, such as bathing, suctioning, on cerebral blood flow velocity?

Which pulse oximeters are most effective in reducing the effects of motion artifact?

Do temperature probe covers contribute to nosocomial infections by providing an environment for skin microbe colonization?

What is the effect of draw-up volume on the accuracy of electrolyte measurements from neonatal arterial lines?

What are the indwell time and catheter-associated complications among EPIV, PICC, and PIV catheters?

Effect of the Environment and Supplemental Stimulation

What is the impact of light, noise, and handling on infants in the NICU?

What is the appropriate level of stimulation for preterm infants?

What is the effect of supplemental massage and gentle touch on preterm infants?

What are the effects of music therapy on preterm infants?

What is the effect of cycled lighting on preterm infants?

What is the most appropriate method of positioning preterm infants to promote neuromuscular development?

Extracorporeal Membrane Oxygenation (ECMO)

Is the initial training and ongoing education of ECMO specialists sufficient to maintain emergency management skills?

What are the long-term effects of ECMO use?

What are the neurodevelopmental outcomes of infants who were treated with ECMO?

Endotracheal Tube Stabilization and Maintenance

How can slippage of the endotracheal tube within the trachea be measured?

How can movement of the endotracheal tube be minimized?

Is there a difference in the incidence of nosocomial infections, bronchopulmonary dysplasia, or frequency of suction when using closed versus open tracheal suctioning in neonates?

Management of Pain

How can neonatal pain be assessed?

When is pharmacologic treatment appropriate?

What factors influence preterm infants' responses to painful procedures?

Are there long-term consequences of unrelieved pain experienced in the neonatal period?

What is the most effective method for weaning the infant from analgesics?

(*continued*)

Box 41.3

SOME CURRENT NEONATAL NURSING RESEARCH QUESTIONS (*continued*)

Management of Pain (*continued*)

Does the use of premedication prior to intubation result in fewer signs of physiologic distress during intubation compared to intubation without premedication?

What are effective nonpharmacologic pain-management techniques for use with neonates?

What are the analgesic effects of oral sucrose and pacifier use on preterm infants during painful procedures?

Thermoregulation

Which techniques are most effective in minimizing insensible water loss and maintaining thermoregulation in the extremely premature infant?

What are the optimal procedures for maintaining thermoregulation when transferring infants from incubators or warmers to open cribs?

What are the effects of skin-to-skin holding (kangaroo care) on thermoregulation of preterm infants?

Positioning and Holding

Which positions are most effective in promoting optimal oxygenation and in minimizing postural deformities?

What are the effects of skin-to-skin holding on high-risk infants?

What are the effects of containment and swaddling of preterm infants?

How often should infants' positions be changed?

Under what conditions is the prone position linked to sudden infant death syndrome?

What factors influence parents' decisions about sleep positions of their infants?

Developmental Care

What are the outcomes of developmental care?

What are the effects of developmental care training programs on the care delivered by NICU staff?

What are valid and reliable measures of stress in preterm infants?

Is measurement of heart rate variability or vagal tone a reliable means for assessing stability or stress in preterm infants?

Do nursing interventions have an effect on preterm infant oxytocin release and contribute to preterm infant neurobiology?

Effects of Cocaine

How is the behavior of a cocaine-exposed infant different from that of the nonexposed infant?

What is the appropriate level of environmental stimulation for these infants?

What types of intervention programs are effective for families of cocaine-exposed infants following hospital discharge?

Effective Parent Teaching Techniques

What are the most effective teaching methods for instructing parents in the care of their newborns?

Is computer-assisted instruction effective?

What type of posthospital follow-up is most helpful to parents of infants who are released from the NICU?

Are postdischarge telephone follow-up programs effective in promoting breastfeeding of preterm infants discharged from the NICU?

What are parents' perceptions of a parental care-by-parent program before NICU discharge of their infants?

Family Issues

What nursing interventions help reduce stressors experienced by families who have infants in the NICU?

What is the incidence of depression among parents of preterm infants?

What interventions help grieving parents?

What interventions help to promote attachment and adaptive parenting between parents and preterm infants and between parents and infants with serious health problems?

What are the outcomes associated with participation in a parent support group for parents of preterm infants?

What are parents' perceptions of the NICU follow-up clinic?

(*continued*)

Box 41.3

SOME CURRENT NEONATAL NURSING RESEARCH QUESTIONS (*continued*)

Staff Education

What is the most effective method of orientation of new NICU nurses?

How should formal classroom teaching and clinical preceptorship be integrated?

Are self-paced learning modules an effective teaching methodology for neonatal nurses?

Can neonatal nurses use expert systems to support decision making?

Delivery of Nursing Care

What is the most effective model for delivery of nursing care in the NICU?

Can nonprofessional staff be used in the NICU to support the professional nurse?

Does the use of critical pathways facilitate "costing out" nursing services?

What is the effect of a structured neonatal resuscitation program on delivery room resuscitation practices?

What are the best strategies to promote use of evidence-based practice guidelines in the NICU setting?

What is the prevalence and severity of secondary traumatic stress in nurses caring for critically ill infants in the NICU?

Retention of Nurses in the Critical Care Setting

What are the factors that increase job satisfaction for nurses working in the NICU?

How do NICU nurses cope with stress?

What factors increase the likelihood that nursing jobs will be retained?

Do neonatal nurses perceive technology in the NICU as sources of stress?

What are the stressors, satisfiers, and coping processes of neonatal nurses?

ECMO, extracorporeal membrane oxygenation; EPIV, extended dwell peripheral intravenous; NICU, neonatal intensive care unit; PICC, peripherally inserted central catheter; PIV, peripheral intravenous.

research-based protocols that could be tested in multiple settings (Gennaro, 1994). Members of the AWHONN Research Committee recommended that the organization fund an EBP project to evaluate the best method for transition of preterm infants to open cribs, appointing a group of six neonatal nurse researchers to conduct the project (Meier, 1994). After reviewing the literature on the topic, the group held a series of meetings and ultimately developed a weaning protocol that was subsequently tested with 270 infants from 10 different hospitals (Medoff-Cooper, 1994). The evidence of this project suggested that preterm infants could be moved to an open crib at lower weights than had been suggested by results of previous studies. The AWHONN project is an excellent example of the contributions that clinical professional associations can make to the development of EBP guidelines. That project illustrates several points in the Star Model: evaluation of original research related to thermoregulation, developing a practice guideline based on a review and synthesis of the existing research, and evaluating the outcome of the EBP guideline.

The AWHONN has implemented two other EBP initiatives to enhance evidence-based neonatal nursing care: (1) development of a protocol for neonatal skin care in association with the National Association of Neonatal Nurses (NANN); and (2) development of guidelines for care of late preterm infants (Medoff-Cooper, Bakewell-Sachs, Buus-Frank, & Santa-Donato, 2005). In the neonatal skin care project, a group of researchers reviewed extant literature to develop a CPG and data collection tools that were implemented by 51 sites involving 2,820 infants in all levels of care. Results of their study indicated that the use of the clinical guideline resulted in improved skin condition of neonates in intensive, secondary, and well-baby nurseries. Nurses also were better able to identify risk factors for impaired skin integrity in neonates.

The Late Preterm Infant Initiative (LPTI) project was launched in April 2005 by AWHONN to develop a research-based guideline (RBG) for infants born between 34 and 37 weeks' postmenstrual age. The initiative was based on a conceptual framework that focuses on neonatal physiologic functional status, nursing care practices, the neonatal care environment, and the role of the family (Medoff-Cooper et al., 2005). A sample of 15 geographically and demographically diverse sites participated in implementing and evaluating the RBG. The focus of this initiative was to enhance awareness of the special needs of the near-term infant among healthcare providers and consumers, and promote universal adoption of a practice guideline for care of these infants. For more information on this initiative, readers can go to the AWHONN website at https://www.awhonn.org/page/AWHONNLateInfant/AWHONN-Late-Preterm-Infant-Initiative.htm

The NANN has published position statements on various practice issues on its website (http://nann.org/about/position-statements). Examples include medication safety in the neonatal intensive care unit (NICU), palliative care for newborns and infants, the use of human milk and breastfeeding in the NICU, cobedding of twins or higher-order multiples, and prevention of bilirubin encephalopathy and kernicterus. In addition, and importantly, the Council of International Neonatal Nurses (COINN; Kenner & Boykova, 2014) has united neonatal nurses through policy work, education, research, and conferences. COINN has been involved in sharing EBP findings across the world.

Barriers and Facilitators to Implementing Neonatal Nursing EBP

Several studies have been conducted to evaluate the extent to which neonatal nurses are implementing EBP guidelines such as

the AWHONN/NANN guidelines. For example, Johnson and Maikler evaluated the implementation of the skin care guidelines in a sample of 136 nurses from 26 hospitals, and identified several barriers to implementing the guidelines in practice: perception by some nurses that traditional practices were superior to the practices proposed by the evidence-based guidelines, difficulty in reading and understanding research evidence, lack of authority to implement the protocols, and lack of physician support (Johnson & Maikler, 2001). Wallin, Boström, Harvey, Wikblad, and Ewald (2000) conducted a similar study in Sweden to determine the extent to which national guidelines on evidence-based nursing care were being implemented in Swedish neonatal units. A total of 13 evidence-based guidelines were developed in cooperation with 42 of the 45 neonatal units in Sweden, and the guidelines were presented in a report that summarized the evidence supporting each guideline, as well as suggested measures for auditing the implementation of the guideline. Findings from this Swedish study indicated that 14.3% of the neonatal units were not using the guidelines at all, and there was variable implementation of the guidelines in the other units. Four factors that were associated significantly with guideline implementation were the extent to which the units were using a quality improvement method, the length of experience of the nurse manager, the level of research experience in the unit, and the availability of nursing staff resources.

Melnyk, Fineout-Overholt, Stone, and Ackerman (2000) surveyed 160 nurses and found that only 46% of these nurses identified their current practices as evidence-based. Factors associated with increased evidence-based care were nurses' beliefs about the importance of EBP, knowledge of EBP, length of practice as an advanced practice nurse, use of the *Cochrane Database of Scientific Reviews* and/or the National Guideline Clearinghouse, and having a mentor to model EBP. Barriers to EBP included lack of time and heavy patient loads; lack of appreciation for the value of research; difficulty searching for and retrieving studies; difficulty reading, understanding, and evaluating research reports; institutional barriers; and limited autonomy or control over one's own practice. Institutional barriers included inadequate staffing and failure to reward nurses who initiated change based on findings from research.

To address the barriers to EBP effectively, neonatal nurses must receive education regarding the research process, have the opportunity to participate in research projects (in data collection or as research participants), and participate with colleagues in sessions to stimulate the formulation of questions from their clinical experience. One can begin by asking the question "why?" of every NICU nursing practice. Lack of resources—including time, money, and consultation—can be more difficult to address. In many institutions, the conduct of nursing research continues to be viewed as unnecessary and not central to the delivery of patient care. In such settings, nurses who wish to conduct research initially might need to invest their own time and money. However, once the research process has demonstrated clinical relevance, additional resources are often made available. Collaboration with colleagues within the institution, schools and universities, and industry can enhance resources. Writing grants with colleagues for the purposes of obtaining funding to support research is often the only way that clinical research can be conducted (Holtzclaw, Kenner, & Walden, 2018).

Mariano et al. (2009) evaluated the effects of mentoring on the EBP of a sample of 20 NICU nurses. Although the researchers were not able to demonstrate changes in EBP of the nurses, they did report changes in the NICU as a result of the project.

There is a need for ongoing research to monitor the extent to which neonatal nurses and nurseries use evidence-based guidelines in practice, and to identify facilitators and barriers to such implementation that should be addressed to ensure continuous quality improvement in neonatal nursing care. In order to facilitate data collection for these studies, it is important to first identify core measures that can be collected and recorded by neonatal units and that can be used to evaluate implementation of EBP guidelines. For example, in 2009, Coughlin, Gibbins, and Hoath (2009) developed a set of such core measures that could be used to evaluate the implementation of evidence-based guidelines for developmentally supportive care in neonatal care. The core measures represent five categories of developmental care that were identified based on an extensive literature review of effective developmental care practices: (1) protected sleep, (2) pain and stress assessment/management, (3) developmentally supportive activities of daily living, (4) family-centered care, and (5) the healing environment.

Conducting Research in Neonatal Nursing

Scientific substantiation of neonatal nursing practice and neonatal healthcare requires collaboration with other nurses and health professionals. Clinical nurses are often the first to recognize and identify trends in newborn and infant care problems for which there is no apparent evidential base. With the guidance and assistance of other nurses, nurse specialists, and physicians, a collaborative investigation can be used to explore such care problems. The combination of expertise from multiple disciplines can make a highly effective research team.

Research is a formal, systematic inquiry or examination of a given problem. The outcome or goal of research is to discover new information or relationships or to verify existing knowledge. Other less formal definitions of research focus on the understanding of an event by logically relating it to other events. Some types of research are designed to predict events by relating them empirically to antecedents in time. Still other types of research attempt to control or manipulate an event or procedure to determine its impact on other phenomena (Burns & Grove, 2009). Quality assurance and quality improvement activities often lead to the design and conduct of research. Nurses are often introduced to issues related to objective data collection through quality assurance audits. Issues of clinical consequence that are identified through quality assurance screening can lead to the articulation of research questions. Research principles can also be used in the evaluation of new procedures, protocols, and products. Evaluation is often an integral part of NICU nursing, but it tends to be performed subjectively rather than objectively. Using research methodology to perform evaluation promotes scientific objectivity.

Why Conduct Research?

Using the research process to discover new information or to confirm empirical knowledge allows the growth and evolution of nursing practice. Without research, nursing care would be based on tradition. Without research, the practice of nursing would change slowly and grow little because things would be done the way they have always been done. The failure to conduct research regarding neonatal care has taught nurses some sobering lessons. Judgments of efficacy based on observation of small numbers of infants or of treatments based on the principle "if a little is good, more is better" have resulted in significant morbidity and mortality for neonates. Increasing the risk of dehydration by withholding early feedings, misuse of oxygen therapy, and misuse of vitamin K are examples of failure to conduct research (Ramachandrappa & Jain, 2008). From these experiences, the use of clinical research trials to evaluate new therapies scientifically has become more common in neonatal care before widespread application. The research

process also provides a vehicle for challenging accepted routines and theories. Nurses caring for neonates often identify issues for which adequate scientific information on which to base clinical judgments does not exist.

VARIOUS RESEARCH ROLES FOR NEONATAL NURSES

The many different research roles for neonatal nurses include research consumer, participant, facilitator/coordinator, and investigator (Harrison, 2001). There is variability in the research roles that are considered appropriate for nurses across the globe. In some countries with limited opportunities for nurses to pursue doctoral degrees, nurses prepared at the master's level are expected to serve as research investigators, whereas in the United States, the investigator role is generally reserved for nurses with doctoral-level education (Harrison, Hernandez, Cianelli, Rivera, & Urrutia, 2005a).

In the United States, the American Association of Colleges of Nursing (AACN) has published a series of "Essentials" guidelines that outline specific competencies for nurses in baccalaureate, master's, and Doctor of Nursing Practice (DNP) programs. The competencies related to research suggest that nurses prepared at the baccalaureate level use evidence to guide their practice (AACN, 2008). Nurses prepared at the master's level translate evidence to improve practice (AACN, 2011). Nurses prepared at the DNP level conduct application-oriented scholarly projects, as opposed to the knowledge-generating research expected of nurses in PhD programs. DNP nurses are prepared to lead EBP initiatives (AACN, 2006). The American Nurses Association (ANA) asserts that all nurses are responsible for assuming various research activities and roles as appropriate to their education (ANA, 2010). The ANA has also created a research toolkit that is available online to help nurses provide evidence-based care (ANA, 2012).

All neonatal nurses should be knowledgeable consumers of research, read reports of research, and ensure that their practice is research- or evidence-based. To be a knowledgeable research consumer, the nurse must be a critical reader of research articles. A rigorous critique of research should also be carried out before one tries to apply the findings in a practice situation. Strategies that might be implemented to assist nurses with developing critical appraisal skills include journal clubs or workshops (Horsley et al., 2011).

Another key research role for every neonatal nurse is to serve as an advocate for infants and families who are research participants to ensure that their rights are protected and that their safety is ensured. Thomas (2005) reviewed ethical and safety issues related to research with vulnerable infants and their families, and suggested that neonatal nurses may serve an important role by reporting any safety concerns to the Institutional Review Board (or ethics committee) that originally approved the study.

Neonatal nurses can also participate in research as data collectors or clinical research coordinators (CRCs). CRCs assume primary responsibility for implementing clinical studies and protocols that are critical for the successful implementation of any study (McKinney & Vermeulen, 2000). With the rapid expansion of global research, and translational research, there is a growing demand for well-prepared CRCs, although there is considerable variability in the specific responsibilities, training, and titles of nurses who work in clinical and/or translational research (Jones, Jester, & Harrison, 2006; Jones, Wilson, Carter, & Jester, 2009). The International Association of Clinical Research Nurses (CRNs) was formed to support the professional and educational needs of CRNs, and is working to identify specific competencies and standards to guide the educational preparation of CRNs (International Association of Clinical Research Nurses, 2012). The Association for Clinical Research Practitioners (ACRP) has a certification program for CRCs as well as for Clinical Research Associates. (Refer to the ACRP website at www.acrpnet.org for more information.) Several nursing schools have started master's level programs to prepare nurses for these roles (Harrison, Hernandez, Cianelli, Rivera, & Urrutia, 2005b; see the website for the University of Alabama at Birmingham School of Nursing for a description of one such program).

Another method of participating in the research process is to perform secondary analyses on data that were collected to answer another research question. Often answers to additional research questions can be extracted from a single database without having to collect new data. Caution, however, must be used in the design of secondary analysis studies to minimize threats to validity and reliability inherent in the method. Neonatal nurses also might promote research by coordinating research committees, promoting research utilization, coordinating research activities in the NICU, and providing educational programs to help nurses understand and use findings from research.

CURRENT TRENDS IN NEONATAL NURSING RESEARCH

Over the past 30 years, there has been a tremendous increase in the quantity and quality of descriptive as well as experimental and quasi-experimental studies focused on preterm or other high-risk infants and their families. Holditch-Davis and Black (2003) reviewed nursing research on the care of preterm infants and identified 17 nurse researchers who had developed programs of neonatal research, meaning that the researcher had at least five publications since 1990 and was the first author on at least three of these publications. These programs of research had four themes: (1) infant responses to the NICU environment, (2) pain management, (3) infant stimulation, and (4) infant behavior and development. Holditch-Davis and Black suggested that these research programs had many strengths, including interdisciplinary focus and clinical relevance, but recommended that more studies should focus on critically ill infants and be based on a developmental science perspective.

Another trend in neonatal research is the publication of reports of EBP projects in the NICU. For example, Pollock and Franklin (2004) described an ongoing project to implement developmentally sensitive care in the NICU. Smith (2005) described the process of developing, implementing, and evaluating a feeding guideline for very low birth weight infants. Three other examples of NICU EBP projects are (1) evaluation of the use of heparinized saline versus normal saline for the maintenance of intravenous access in neonates (Cook, Bellini, & Cusson, 2011); (2) evaluation of the effect of toys in the NICU microenvironment on nosocomial infection rates (Hanrahan & Lofgren, 2004); and (3) proposing evidence-based guidelines for kangaroo care in the NICU (Ludington-Hoe, 2011).

An important source of funding for nursing research is the NINR, an institute within the U.S. Department of Health and Human Services (DHHS) National Institutes of Health (NIH). Abstracts of research funded by the NIH can be searched and retrieved in the Research Portfolio Online Reporting Tools (RePORT) database (http://projectreporter.nih.gov/reporter.cfm). A query using the keywords "neonatal nursing" resulted in a listing of 21 abstracts of research funded by the NIH (National Institutes

of Health, 2018b). Table 41.5 lists examples of these funded studies.

There are many opportunities for neonatal nurses to implement EBP projects to improve the quality of care for patients and families. Sharing experiences through presentations at professional meetings or publication in the professional literature will contribute to the growing body of information about EBP and the implementation of evidence-based neonatal nursing practice.

TABLE 41.5

EXAMPLES OF STUDIES RELATED TO NEONATAL NURSING FUNDED BY THE NATIONAL INSTITUTES OF HEALTH IN 2017–2018

Principal Investigator	Organization	Title of Study
Katherine E. Gregory	Brigham and Women's Hospital	The influence of the milk microbiome on inflammation of the preterm infant
Tondi M. Harrison	The Ohio State University	Behavioral and physiological responses to oral feeding in infants with complex congenital heart disease
James L. McManaman	University of Colorado, Denver	Postnatal actions of maternal obesity on neonatal metabolic health
Marliese D. Nist	The Ohio State University	Inflammatory mediators of stress exposure and neurodevelopment in very preterm infants
Jochen Profit	Stanford University	Social disparities in NICU care
Jochen Profit	Stanford University	The WISER study
Lisa S. Segre	University of Iowa	Promoting emotional well-being in distressed NICU mothers: A phase 2 evaluation of a nurse-delivered approach
Heather L. Tubbs-Cooley	Cincinnati Children's Hospital Medical Center	Systems analysis of guideline adherence in neonatal intensive care

NICU, neonatal intensive care unit.

Source: From the National Institutes of Health. (n.d.). Project search results for neonatal nursing. Retrieved from http://projectreporter.nih.gov/reporter_searchresults.cfm

SUMMARY

With more and more hospitals and healthcare organizations striving for Magnet status and the inclusion of evidence-based clinical guidelines for care in these institutions, research, research utilization, and EBP reviews and guidelines will continue to grow. This chapter has highlighted some of the ways neonatal nursing care is being impacted through EBP and research.

EVIDENCE-BASED PRACTICE BOX

For the past 20 years, neonatal researchers have conducted studies to assess the effects of music and music therapy provided to preterm infants in the NICU. Hodges and Wilson (2010) published an integrative review of 35 of these studies, which is an example of an evidence summary (the second category in the five-point Star Model of Transformation). The authors concluded that comparison of results from the studies was difficult because of the wide variations in type of music, volume, duration, and gestational ages of the infants. However, despite the limitations, findings from many of the studies suggested positive effects of music on increasing oxygen saturation levels, reducing heart rates and arousal, and improving parent–infant interaction in hospitalized preterm infants. The authors made specific recommendations about future research to address the limitations of existing studies and provide evidence for practice.

Reference

Hodges, A. L., & Wilson, L. L. (2010). Effects of music therapy on preterm infants in the neonatal intensive care unit. *Alternative Therapy Health Medicine, 16*(5), 72–73. Retrieved from http://www.alternative-therapies.com/index.cfm/fuseaction/archives.main

REFERENCES

Adams, K., & Corrigan, J. M. (Eds.). (2003). *Priority areas for national action: Transforming health care quality*. Washington, DC: National Academies of Science.

Agency for Healthcare Research and Quality. (2012a). *National healthcare disparities report 2011*. Washington, DC: U.S. Department of Health and Human Services. Retrieved from https://archive.ahrq.gov/research/findings/nhqrdr/nhdr11/nhdr11.pdf

Agency for Healthcare Research and Quality. (2012b). *National healthcare quality report 2011*. Washington, DC: U.S. Department of Health and Human Services. Retrieved from https://archive.ahrq.gov/research/findings/nhqrdr/nhqr11/nhqr11.pdf

American Association of Colleges of Nursing. (2006). *The essentials of doctoral education for advanced nursing practice*. Washington, DC: Author. Retrieved from https://www.aacnnursing.org/Portals/42/Publications/DNPEssentials.pdf

American Association of Colleges of Nursing. (2008). *The essentials of baccalaureate education for professional nursing practice*. Washington, DC: Author. Retrieved from https://www.aacnnursing.org/Portals/42/Publications/BaccEssentials08.pdf

American Association of Colleges of Nursing. (2011). *The essentials of master's education in nursing*. Washington, DC: Author. Retrieved from https://www.aacnnursing.org/Portals/42/Publications/MastersEssentials11.pdf

American Nurses Association. (2010). *Nursing: Scope and standards of practice*. Silver Spring, MD: Author.

American Nurses Association. (2012). *Research toolkit*. Retrieved from https://www.nursingworld.org/practice-policy/workforce/what-is-nursing/nursing-research/

Association of Women's Health Obstetric and Neonatal Nurses. (2010). Assessment and care of the late preterm infant. Evidence-based clinical practice guideline. Retrieved from http://www.guideline.gov/content.aspx?id=24066&search=association+of+women%e2%80%99s+health%2c+obstetric%2c+and+neonatal+nurses

Burns, N., & Grove, S. K. (Eds.). (2009). *The practice of nursing research: Appraisal, synthesis, and generation of evidence* (6th ed.). Philadelphia, PA: Saunders.

Cook, L., Bellini, S., & Cusson, R. M. (2011). Heparinized saline vs normal saline for maintenance of intravenous access in neonates: An evidence-based practice change. *Advances in Neonatal Care, 11*(3), 208–215. doi:10.1097/ANC.0b013e31821bab61

Coughlin, M., Gibbins, S., & Hoath, S. (2009). Core measures for developmentally supportive care in neonatal intensive care units: Theory, precedence and practice. *Journal of Advanced Nursing, 65*(10), 2239–2248. doi:10.1111/j.1365-2648.2009.05052.x

Eden, J., Levit, L., Berg, A., & Morton, S. (Eds.). (2011). *Finding what works in health care: Standards for systematic reviews*. Washington, DC: National Academies Press.

Eden, J., Wheatley, B., McNeil, B., & Sox, H. (Eds.). (2008). *Knowing what works in health care: A roadmap for the nation*. Washington, DC: National Academies Press.

eGranary Digital Library. (2012). Zambia nursing and midwifery. Retrieved from http://www.widernet.org/digitallibrary/portals/PortalViewer.asp?PortalPageID=492

Gennaro, S. (1994). Research utilization: An overview. *Journal of Obstetric, Gynecologic, & Neonatal Nursing, 23*(4), 313–319. doi:10.1111/j.1552-6909.1994.tb01882.x

Graham, R., Mancher, M., Wolman, D. M., Greenfield, S., & Steinberg, E. (Eds.). (2011). *Clinical practice guidelines we can trust*. Washington, DC: National Academies Press.

Guidelines International Network. (2012). *Introduction*. Retrieved from http://www.g-i-n.net/about-g-i-n

Guyatt, G., Rennie, D., Meade, M., & Cook, D. (2008). *Users guide to the medical literature: A manual for evidence-based clinical practice*. New York, NY: McGraw-Hill Professional.

Hanrahan, K. S., & Lofgren, M. (2004). Evidence-based practice: Examining the risk of toys in the microenvironment of infants in the neonatal intensive care unit. *Advances in Neonatal Care (Elsevier Science), 4*(4), 184–205. doi:10.1016/j.adnc.2004.05.002

Harrison, L. L. (2001). Research roles for neonatal nurses. *Central Lines, 17*(1), 18–20.

Harrison, L. L., Hernandez, A. R., Cianelli, R., Rivera, S., & Urrutia, M. (2005a). Competencias en investigación para diferentes niveles de formación de enfermeras: Una perspectiva latinoamericana. *Ciencia y Enfermería, XI*(1), 59–71. doi:10.4067/S0717-95532005000100007

Harrison, L. L., Hernandez, A. R., Cianelli, R., Rivera, S., & Urrutia, M. (2005b). Perspectives of Latin American nursing professors and leaders about research competencies needed by nurses with different levels of academic preparation. *International Journal of Nursing Education Scholarship, 2*(1), 24. doi:10.2202/1548-923X.1126

Higgins, J. P. T., & Green, S. (Eds.). (2011). *Cochrane handbook for systematic reviews of interventions* (version 5.1.0). Retrieved from http://handbook-5-1.cochrane.org/

HINARI Access to Research for Health Programme. (n.d.). *About HINARI*. Retrieved from http://www.who.int/hinari/about/en

Holditch-Davis, D., & Black, B. P. (2003). Care of preterm infants: Programs of research and their relationship to developmental science. *Annual Review of Nursing Research, 21*, 23–60. doi:10.1891/0739-6686.21.1.23

Holtzclaw, B. J., Kenner, C., & Walden, M. (2018). *Grant Writing Handbook for Nurses and Health Professionals* (3rd ed.). New York, (NY): Springer Publishing Company.

Horsley, T., Hyde, C., Santesso, N., Parkes, J., Milne, R., & Stewart, R. (2011). Teaching critical appraisal skills in healthcare settings. *Cochrane Database of Systematic Reviews*, (11), CD001270. doi:10.1002/14651858.CD001270.pub2

Improvement Science Research Network. (2010). Research priorities. Retrieved from https://journals.lww.com/jbipacesetters/Citation/2010/07000/Improvement_Science_Research_Network.7.aspx

Institute of Medicine. (2001). *Crossing the quality chasm: Healthcare for the 21st century*. Washington, DC: National Academies of Science.

Institute of Medicine. (2011). *The future of nursing: Leading change, advancing health*. Washington, DC: The National Academies Press.

Institute of Medicine (2013). *Crossing the quality chasm: The IOM health care quality initiative*. Retrieved from http://www.nationalacademies.org/hmd/Global/News%20Announcements/Crossing-the-Quality-Chasm-The-IOM-Health-Care-Quality-Initiative.aspx

International Association of Clinical Research Nurses. (2012). About IACRN. Retrieved from http://iacrn.memberlodge.org/Default.aspx?pageId=505167

Johnson, F. E., & Maikler, V. E. (2001). Nurses' adoption of the AWHONN/NANN neonatal skin care project. *Newborn & Infant Nursing Reviews, 1*(1), 59–67. doi:10.1053/nbin.2001.21831

Jones, C. T., Jester, P. M., & Harrison, L. (2006). Clinical research in low resource countries. *Research Practitioner, 7*(6), 188–199.

Jones, C. T., Wilson, L. L., Carter, S., & Jester, P. M. (2009). Development and implementation of a distance-learning certificate program in clinical research management at international sites. *Southern Online Journal of Nursing Research, 9*(3), 1–16. Retrieved from https://www.snrs.org/sites/default/files/SOJNR/2009/Vol09Num03Art09.pdf

Kenner, C., & Boykova, M. (2014). COINN: Neonatal nurses making a difference globally. *Newborn and Infant Nursing Reviews, 14*, 4–6. doi:10.1053/j.nainr.2013.12.005

Kohn, L. T., Corrigan, J. M., & Donaldson, M. S. (Eds.). (2000). *To err is human: Building a safer health system*. Washington, DC: National Academies Press.

Ludington-Hoe, S. M. (2011). Thirty years of kangaroo care science and practice. *Neonatal Network, 30*(5), 357–362. doi:10.1891/0730-0832.30.5.357

Mariano, K. G., Caley, L. M., Eschberger, L., Woloszyn, A., Volker, P., Leonard, M. S., & Tung, Y. (2009). Building evidence-based practice with staff nurses through mentoring. *Journal of Neonatal Nursing, 15*(3), 81–87. doi:10.1016/j.jnn.2009.01.005

McKinney, J., & Vermeulen, W. (2000). Research nurses play a vital role in clinical trials. *Oncology Nursing Forum, 27*(1), 28.

Medoff-Cooper, B. (1994). Transition of the preterm infant to an open crib. *Journal of Obstetric, Gynecologic & Neonatal Nursing, 23*(4), 329–335. doi:10.1111/j.1552-6909.1994.tb01884.x

Medoff-Cooper, B., Bakewell-Sachs, S., Buus-Frank, M. E., & Santa-Donato, A. (2005). The AWHONN Near-Term Infant Initiative: A

conceptual framework for optimizing health for near-term infants. *Journal of Obstetric, Gynecologic and Neonatal Nursing, 34*(6), 666–671. doi:10.1177/0884217505281873

Meier, P. P. (1994). Transition of the preterm infant to an open crib: Process of the project group. *Journal of Obstetric, Gynecologic and Neonatal Nursing, 23*(4), 321–326. doi:10.1111/j.1552-6909.1994.tb01883.x

Melnyk, B. M., Fineout-Overholt, E., Stone, P., & Ackerman, M. (2000). Evidence-based practice: The past, present, and recommendations for the millennium. *Pediatric Nursing, 26*(1), 77–81.

Mulrow, C. (1994). Rationale for systematic reviews. *British Medical Journal, 309*, 597–599. doi:10.1136/bmj.309.6954.597

National Institute of Nursing Research. (2011). *Bringing science to life: NINR strategic plan*. Bethesda, MD: Author. Retrieved from https://www.ninr.nih.gov/sites/files/docs/ninr-strategic-plan-2011.pdf

National Institute of Nursing Research (2016). *The NINR strategic plan: Advancing science, improving lives: A vision for nursing science*. Bethesda, MD: Author. Retrieved from https://www.ninr.nih.gov/sites/files/docs/NINR_StratPlan2016_reduced.pdf

National Institutes of Health. (n.d.). Project search results for neonatal nursing. Retrieved from http://projectreporter.nih.gov/reporter_searchresults.cfm

Pollock, T. R., & Franklin, C. (2004). Use of evidence-based practice in the neonatal intensive care unit. *Critical Care Nursing Clinics of North America, 16*(2), 243–248. doi:10.1016/j.ccell.2004.02.006

Ramachandrappa, A., & Jain, L. (2008). Iatrogenic disorders in modern neonatology: A focus on safety and quality of care. *Clinics in Perinatology, 35*(1), 1–34. doi:10.1016/j.clp.2007.11.012

Rogers, E. M. M. (1995). *Diffusion of innovations* (4th ed.). New York, NY: The Free Press.

Sackett, D. L., Straus, S. E., Richardson, W. S., Rosenberg, W., & Haynes, R. B. (2000). *Evidence-based medicine: How to practice and teach EBM* (2nd ed.). Edinburgh, UK: Churchill Livingstone.

Smith, J. R. (2005). Early enteral feeding for the very low birth weight infant: The development and impact of a research-based guideline. *Neonatal Network, 24*(4), 9–19. doi:10.1891/0730-0832.24.4.9

Stevens, K. R. (2004). ACE Star Model: Cycle of knowledge transformation. Retrieved from http://www.acestar.uthscsa.edu

Stevens, K. R. (2009). *Essential competencies for evidence-based practice in nursing*. San Antonio: University of Texas Health Science Center.

Stevens, K. (2013, May 13). The impact of evidence-based practice in nursing and the next big ideas. *OJIN: The Online Journal of Issues in Nursing, 18*(2), 4. doi:10.3912/OJIN.Vol18No02Man04

Stevens, K. R. (2015). *Star Model of EBP: Knowledge transformation*. Academic Center for Evidence-Based Practice, San Antonio: The University of Texas Health Science Center at San Antonio.

Stevens, K. R., Pepper, G. A., Horn, S. D., & Mitchell, S. A. (2017). Evidence-based practice and practice-based evidence and informatics. In R. Nelson & N. Staggers (Eds.), *Health informatics: An interprofessional approach* (2nd ed., pp. 38–59). St. Louis, MO: Elsevier.

Stevens, K. R., & Pugh, J. A. (1999). Evidence-based practice and perioperative nursing. *Seminars in Perioperative Nursing, 8*(3), 155–159.

Thomas, K. A. (2005). Safety: When infants and parents are research subjects. *Journal of Perinatal & Neonatal Nursing, 19*(1), 52–58. doi:10.1097/00005237-200501000-00012

Vermont Oxford Network. (2012). What is the Vermont Oxford Network? Retrieved from http://www.vtoxford.org/about/about.aspx

Wallin, L., Boström, A. M., Harvey, G., Wikblad, K., & Ewald, U. (2000). National guidelines for Swedish neonatal nursing care: Evaluation of clinical application. *International Journal for Quality in Health Care, 12*(6), 465–474. doi:10.1093/intqhc/12.6.465

CHAPTER 42

Legal and Ethical Issues in Neonatal Care

Carole Kenner

INTRODUCTION

In the high-technology and often high-tension milieu of the NICU, nurses and other healthcare professionals inevitably encounter ethical issues. However, ethical issues involving neonates are not limited to the NICU. Neonatal nurses are providing comprehensive care in an increasingly complex environment for a very diverse population. These challenges will continue to bring ethical issues to the forefront of neonatal care and will require thoughtful reflection.

Ethical issues are often intertwined with legal considerations, further adding to their complexity. Nurses may experience moral distress related to the complexities of care and associated ethical dilemmas. Neonatal nurses and advanced practice neonatal nurses are well positioned for leadership roles in managing ethical and legal issues in the neonatal care settings. This chapter provides an overview of ethical and legal issues that can arise across the spectrum of neonatal care, as well as approaches to recognizing and managing these issues.

RECOGNIZING ETHICAL ISSUES IN NEONATAL CARE AND THE NICU

The NICU and care of neonates can be laden with ethical issues (Cavaliere, Daly, Dowling, & Montgomery, 2011; Kuschel & Kent, 2011; Orzalesi, 2010). The blurred boundaries for viability, coupled with parental preferences and legal considerations, can lead to ethical issues across the spectrum of neonatal care. One of the challenges faced by neonatal nurses is effectively recognizing ethical issues in the midst of providing complex care.

Some neonatal care issues with ethical implications may be more readily recognizable than others. For example, consider the case of a neonate experiencing deteriorating multisystem organ failure whose parents wish to continue aggressive care. The NICU team may be recommending increased palliative and supportive care measures with a deceleration in other measures. This type of heart-wrenching scenario unfortunately continues to occur and is recognized as a classical NICU ethical issue. Many nurses do not feel they have adequate training/education in palliative care to provide the needed support, and this leads to an ethical dilemma (Gibson, Hofmeyer, & Warland, 2018). It is important for neonatal nurses to examine other neonatal care ethical issues that are not as easily recognizable. If nurses have no role in the team decisions about care, moral distress can occur (Molloy, Evans, & Coughlin, 2015; Thorne, Konikoff, Brown, & Albersheim, 2018).

Parents may express care preferences that are deemed nonpermissible because they fall outside usual care practices and may be believed to be potentially harmful to the neonate. For example, parents may want to burn incense in the mother's hospital room in the presence of their newborn. While hospital policy will likely dictate no candles or other flaming substances for the security of all persons in the building and in consideration of the health of the neonate, it would not be in the family's best interest to end the interaction with a discussion of what is not permissible and why. Rather, it would be important for this neonate's nurse to talk further with the parents about their request. Engaging the parents in dialogue about the issue can provide insight into their beliefs and practice preferences. Through this process, the neonatal nurse and parents together can determine an acceptable alternative. The neonatal nurses' actions will demonstrate respect for their role as parents as well as their preferences. Perhaps most significant, though, is that the neonatal nurses will have established a supportive relationship with the parents as opposed to what could have quickly become an unintended adversarial relationship.

Situations such as the one just described may raise questions among neonatal nurses regarding how to best recognize and manage situations that extend beyond clinical care. To assist in understanding the development of ethical issues, an overview of key ethical principles follows.

ETHICAL PRINCIPLES

It is important for neonatal nurses to understand the ethical principles that can help guide their actions when they encounter an ethical situation. Beauchamp and Childress (2009) specify four key principles for biomedical ethics: autonomy, beneficence, nonmaleficence, and justice. Each of these principles is presented along with examples demonstrating how neonatal nurses can apply them to everyday practice.

The principle of autonomy focuses on an individual's independence and the right to make decisions. In neonatal care, the decision makers are the parents rather than the actual patient. To respect the principle of autonomy, neonatal nurses and other team members should engage the parents in decision making about the neonate's plan of care to the fullest extent possible. For example,

it may be medically indicated for a neonate to undergo surgical ligation of a patent ductus arteriosus. Prior to the surgical team obtaining informed consent for this surgery, the neonatal nurse and other team members can provide ample opportunity for the parents to consider the information provided to them to ensure that all of their questions are addressed.

Beneficence, or doing well, is a principle that along with nonmaleficence (avoiding causing harm) represents optimal nursing care. Neonatal nurses are consistently engaged in care that meets best practice standards for promoting the well-being of the neonate. Adequate positioning, promotion of rest, and other supportive care measures demonstrate care delivery in a beneficent manner. Similarly, the avoidance of causing intentional harm to a neonate illustrates nonmaleficent behavior. Consideration of these two ethical principles provides a supportive foundation for delivering the best possible care.

The ethical principle of justice can be viewed in a multitude of ways in healthcare incorporating varying components of equity, allocation, rationing, and access (Beauchamp & Childress, 2009). An examination of justice in neonatal care can focus on the actual process of care delivery. While neonatal nurses are not responsible for the broader issues of access to care, they are in a position to ensure that the neonates within their care receive similar attention and that the care is prioritized based on need. For example, with the number of neonates experiencing withdrawal symptoms, staffing ratios do not always take into consideration the complexity of this care (Smith, Rogowski, Schoenauer, & Lake, 2018). This scenario requires adjustment of assignments to provide adequate care to a neonate in withdrawal (Smith et al., 2018). Providing care to all neonates without regard for extraneous factors such as socioeconomic status and ethnicity represents an important component of the principle of justice in neonatal care.

MANAGING ETHICAL ISSUES: RESOLUTION STRATEGIES

There are various approaches to managing the types of ethical issues that can arise in neonatal settings. While each neonatal care unit or hospital may have a standardized resolution pathway already in place, it can be helpful to explore alternate approaches. Among the ethical issue–resolution strategies available to neonatal nurses are engaging in nursing and/or healthcare team ethics rounds, debriefing discussions, and consultation and collaboration with hospital ethics committees.

Nursing Ethics Rounds

Among the strategies that neonatal nurses may find helpful when faced with ethical issues are engaging in nursing ethics rounds and team discussions. Nursing ethics rounds (Robichaux, 2012) can assist neonatal nurses to recognize and manage developing issues. Ethics rounds can provide an opportunity for addressing developing issues before they expand in complexity and become emotionally laden for all involved individuals. Additionally, through ethics rounds, neonatal nurses can engage in dialogue and elicit support from team members for any identified issues or care-based concerns.

Debriefing Discussions

Following a particularly complex or emotionally laden care situation, it can be beneficial for all members of the healthcare team to participate in debriefing discussions. These discussions can be requested by any team member, but should be scheduled when the key care providers can be in attendance. It is also helpful to ensure that any providers with dissenting opinions or conflicted views are included in open and nonjudgmental dialogue. The session should include a discussion of the salient ethical issues in the case, allowing all team members to identify their perceived areas of discomfort. For those team members who continue to have unresolved discomfort or distress, additional individualized support needs can be identified and enacted.

Collaborating With Hospital Ethics Committees

Hospital ethics committees generally operate in an advisory capacity and can provide guidance with the ethical issues of cases but not serve in a legal advisory capacity (Mercurio, 2011). In situations where different members of the healthcare team and/or the parents have conflicting perspectives on what will be the best course of action, it can be helpful to obtain the perspectives of individuals not directly involved with the case. Additionally, it is important to consider the perspective of the organization and explore the means to involve others from the organization in the clinical decision-making process as warranted (Bean, 2011).

Aside from providing perspectives on actual cases, ethics committees can assist in a consultative manner to garner perspective on potential issues before they arise. Ethics committees can also assist with reviews of past cases or tenuous situations by examining other pathways than the one taken and laying the foundation for future resolution strategies. Examples of neonatal issues before these committees are use of extracorporeal membrane oxygenation (ECMO) or what constitutes viability—a question that brings many different perspectives to the dialogue (Bucher et al., 2018; Peterec, Bizzarro, & Mercurio, 2018).

SUPPORT FOR THE FAMILY

While neonatal nurses often become engaged in close relationships with families of the neonates they care for, the family may begin to feel isolated when ethical issues arise. During these challenging times, neonatal nurses can exhibit leadership in ensuring that families remain engaged to the fullest extent possible. Supporting families in the NICU encompasses a multitude of actions on behalf of the neonate's parents as well as siblings and extended family members. The neonatal nurse may serve as an advocate for grandparent visitation or assist parents in explaining the complexities of the NICU to the neonate's siblings. Perhaps most importantly, they support parents through ensuring their role in various components of decision making (Kavanaugh, Moro, & Savage, 2010; Sudia-Robinson, 2011b), respecting their role regardless of opposing treatment perspectives (Sudia-Robinson, 2011a), and speaking on their behalf (Spence, 2011) whenever necessary. More research needs to be done to determine how best to involve parents in decision making and to what extent they wish to be included (Richards et al., 2017).

Decision Making

One means of demonstrating respect for parents is involving them in decision making (Rushton, 2007). For parents to truly participate in decision making, they must have the necessary information. Information for decision making should be presented to parents in a manner that is easily understandable, yet at an appropriate level for their education and background experiences. While all parents need baseline information, the kinds of questions that parents ask will provide a good indication of their desire and readiness for additional information. Additionally, by providing information in an objective manner, parents will be in a better position to share their values and perspectives rather than being overly influenced by those of the healthcare team (Kuschel & Kent, 2011). Shared

Box 42.1

INVITATIONAL QUESTIONS AND STATEMENTS

Avoid Yes/No Response Questions

Is there anything you want to know about your baby's progress?

Replace with:

What else would you like to discuss regarding your baby's progress?

Other Open-Ended Questions

What else can I provide more information about?

What questions would you like to ask?

Invitational Statements

This is a lot of information. Let's pause so that you can ask questions.

We presented possible care options. Let's discuss your thoughts about each of them.

Tell me the questions you would like to ask the neonatal care team.

decision making is a cornerstone to family-centered integrative care (Ahlqvist-Björkroth, 2017).

Cultivating an invitational atmosphere will foster dialogue and provide an avenue for parents to be active participants in the decision-making process (see Box 42.1). By assuming that all parents have questions regarding some aspect of their neonate's care, neonatal nurses will keep the door to dialogue open. Invitational atmospheres for dialogue allow parents to ask as many or as few questions as they like. An open atmosphere for questions also provides opportunities for parents to ask questions at a time when they are ready to receive the information. For example, some parents can become overwhelmed when a large amount of information is presented during a single conversation. However, when they are given time to process the information, their questions will emerge and they can further engage in dialogue and decision making. For some parents, the role they play in determining outcomes may not even be as important as the opportunity to engage in the decision-making process (Gallagher, Marlow, Edgley, & Porock, 2011). Ethically sound decisions, collaboratively determined to be in the best interest of the infant, represent best practice (Orzalesi, 2010).

Determining Parental Preferences

While it is important to cultivate an open environment for parental engagement in various aspects of care for their neonate, it is equally important to determine their preferences for such involvement. Some parents will want to be very much involved in decision making while others indicate a preference for varying degrees of delegation. Parental involvement should not be viewed as an all-or-none phenomenon, but rather on a continuum that may change over the course of the neonate's hospitalization (Gillam & Sullivan, 2011). Neonatal nurses can play a key role in assessing parental preferences of involvement in care decisions both at the onset and at key time intervals, such as when the neonate's condition significantly improves or becomes increasingly complex. Communication between health professionals and parents is a critical factor in determining how parents want to be involved in care decisions (Ahlqvist-Björkroth, 2017).

Opposing Points of View

In the increasingly complex care environment of NICUs, there will inevitably be varying perspectives on care decisions between parents and the healthcare team. Parents may hold different points of view regarding the overall treatment plan or specific components of care. Neonatal nurses can assist in bridging these differences by engaging parents in conversation about these issues and their preferences. Learning more about their perspective and desired outcomes can lead to improved communication and enhanced decision making (Ahlqvist-Björkroth, 2017; Gillam & Sullivan, 2011; Sudia-Robinson, 2011b).

In situations where parents and the healthcare team are in disagreement about major care issues, it is important for the neonatal nurse to foster continued parental engagement in decision making to the greatest extent possible. For example, a situation may arise where despite the parents' expressed preferences, continued aggressive care is deemed appropriate. The parents can still be encouraged to be involved in other decision making about the care of their neonate such as touch time scheduling. Neonatal nurses can ask parents about their preferences in the scheduling of limited touch times, ensuring that some of those times are when the parents indicate that they can be present at the bedside. Sometimes even relatively minor decision-making opportunities can help restore respect for their role as parents and enhance feelings of connection with their neonate.

SUPPORT FOR THE NEONATAL NURSE

While neonatal nurses are actively engaged in supporting neonates, their parents, and their extended family members, they may neglect their personal needs for health and well-being. Attention to personal care needs is especially important for nurses working in settings that can be physically, mentally, and emotionally challenging. Neonatal nurses need to advocate for their own needs just as they do for the needs of the neonates and families they care for. Actively expressing their needs and taking steps to support themselves, colleagues, and other members of their team are key components of self-sustainability and effective care delivery. Without adequate support, untoward issues can arise for neonatal nurses and other team members. Additionally, during particularly challenging patient and family situations, neonatal nurses may find themselves feeling undue stress with related manifestations, such as compassion fatigue and moral distress.

Compassion Fatigue

Compassion fatigue and emotional exhaustion among nurses have been attributed to a variety of factors including stressful work environments, additional nursing care responsibilities and priority conflicts, extensive and intensive work hours, role responsibilities, and emotionally laden patient care situations (Boyle, 2011; Garcia & Calvo, 2011; McGibbon, Peter, & Gallop, 2010; Potter et al., 2010; Yoder, 2010). This is an evolving area of interest among both nurse administrators and researchers as they strive to develop interventions to support nurses who have experienced compassion fatigue and to develop preventive measures. For neonatal nurses, potential mitigating interventions include on-site professional counseling services, art therapy, rotating patient assignments, extra days off, spiritual support, grief resolution, and self-care goals with specified plans to achieve them (Boyle, 2011; Coetzee & Klopper, 2010; Yoder, 2010). When there is self-compassion, a strong relationship between the nurse and family, and interprofessional–physician nurse collegiality, there is less compassion fatigue (Sano, Schiffman, Shoji, & Sawin, 2018). Strategies to encourage

these attributes may decrease the exhaustion and compassion fatigue nurses often feel.

Moral Distress

Moral distress among nurses and other healthcare professionals can occur when they cannot enact what they perceive as the right or correct thing to do (Callister & Sudia-Robinson, 2011; Pauly, Varcoe, Storch, & Newton, 2009). Acknowledging feelings of moral distress in oneself as well as recognizing moral distress among team members is an important component in the process of ethical care delivery. Signs of moral distress can include feeling conflicted about care decisions and uncomfortable with a lack of involvement in care decisions. Moral distress is linked with the development of depression (Lamiani, Dordoni, & Argentero, 2017). Attention to these feelings is important for both the neonatal team morale and overall care delivery (Janvier, Nadeau, Deschenes, Couture, & Barrington, 2007).

The American Association of Critical-Care Nurses (AACN, 2008) presented a framework for nurses to manage moral distress, referred to as the four A's: ask, affirm, assess, and act. The first A, ask, focuses on the nurse asking oneself questions to determine if distress is present within oneself and/or the healthcare team. Next, through affirming, the nurse validates the feelings of distress by exploring with others. The third step involves assessing the source of the distress and determining that an action plan is needed. Through the fourth step, the nurse develops and implements an action plan. The four A's framework is circular rather than linear, indicating the need to revisit steps as the plan unfolds and to develop additional strategies as needed. One book that addresses moral distress is *Moral Distress in the Health Professions* by Ulrich and Grady (2018).

Strategies that neonatal nurses can utilize to manage moral distress within themselves and team members include verbalizing their concerns and feelings of distress through story telling (Austin, Kelecevic, Goble, & Mekechuk, 2009) and other means of sharing with team members. Further, journal clubs focused on the review of ethical issues, as well as case studies, can help neonatal nurses be better prepared when confronted with ethical issues (Garity, 2009).

LEGAL ISSUES

Neonatal nurses, as well as staff nurses and the nurse practitioner, may be involved in malpractice suits. Most of these instances involve a perinatal event, a neonatal event, or a combination. The types of cases range from a medication error to catastrophic outcomes—death or lifetime disabilities. The cause may be a perinatal event whose effects are not seen until the infant is in the NICU. It could also be a high bilirubin that is not aggressively addressed, or signs of temperature, heart or respiratory rate, or oxygen saturations that are outside of the normal range for a while. Other potential possibilities include a prolonged resuscitation with bad neurological outcomes or a failure to provide an adequate airway (Giuseppe, Riccardo, & Del Sordo, 2018). The lawsuit generally includes the physicians, nurses, and the hospital. Although hospital malpractice does cover all employees, nurses can also obtain their own malpractice insurance; that attorney will then be charged with looking out solely for the nurse's best interests. The choice of whether or not to have personal insurance is left up to the individual nurse. So how does a nurse protect against a lawsuit? The nurse should make sure the policies and procedures of the institute are followed and that there is good documentation of what is done. If there appears to be a problem, the nurse should document and follow the chain of command, as this will record that the nurse has notified others of a situation. If a mistake is made, the nurse should follow the institutional policies for such events and get advice from risk management if that is possible. If a lawsuit is brought and involves the nursing care, the nurse should make sure to know his or her rights and seek legal advice. Remember that emails are discoverable, so nurses should be careful what is put in an email. Nurses can also make notes for themselves to document details that might not be in the chart—impressions they may have at the time. Nurses should keep them in a secure place for their own use.

SUMMARY

Neonatal nurses are uniquely positioned to serve as leaders and supporters of all aspects of ethical care delivery. Assisting parents to express their preferences for care delivery and providing support for those preferences to the greatest extent possible are components of practicing within an ethical context. Through the delivery of highly skilled bedside care to facilitating parental involvement in care-based dialogue and decision making, neonatal nurses enact key advocacy roles for neonates and their parents.

ONLINE RESOURCES

The current legal climate in neonatology. (2008). *Medscape.* Retrieved from https://www.medscape.org/viewarticle/568009

The Hastings Center. (n.d.). Hastings Center Bioiethics Briefings: For Journalists, Policymakers, and Educators. Retrieved from https://www.thehastingscenter.org/briefingbook/neonatal-care

Winning, A. M., Merandi, J. M., Lewe, D., Stepney, L. M. C., Liao, N. N., Fortney, C. A., & Gerhardt, C. A. (2018). The emotional impact of errors or adverse events on healthcare providers in the NICU: The protective role of coworker support. *Journal of Advanced Nursing*, *74*(1), 172–180. doi:10.1111/jan.13403

REFERENCES

Ahlqvist-Björkroth, S. (2017). Communication between healthcare professionals and parents is a key factor in involving parents in neonatal intensive care. *Acta Pædiatrica, 107*(1), 12–13. doi:10.1111/apa.14111

American Association of Critical-Care Nurses. (2008). *The 4A's to rise above moral distress*. Retrieved from https://www.emergingrnleader.com/wp-content/uploads/2012/06/4As_to_Rise_Above_Moral_Distress.pdf

Austin, W., Kelecevic, J., Goble, E., & Mekechuk, J. (2009). An overview of moral distress and the paediatric intensive care team. *Nursing Ethics, 16*(1), 57–68. doi:10.1177/0969733008097990

Bean, S. (2011). Navigating the murky intersection between clinical and organizational ethics: A hybrid case taxonomy. *Bioethics*, *25*(6), 320–325. doi:10.1111/j.1467-8519.2009.01783.x

Beauchamp, T., & Childress, J. (2009). *Principles of biomedical ethics*. (6th ed.). New York, NY: Oxford University Press.

Boyle, D. A. (2011). Countering compassion fatigue: A requisite nursing agenda. *Online Journal of Issues in Nursing, 16*(1), 1–20. doi:10.3912/OJIN.Vol16No01Man02.

Bucher, H. U., Klein, S. D., Hendriks, M. J., Baumann-Hölzle, R., Berger, T. M., Streuli, J. C., & Fauchère, J.-C.(2018). Decision-making at the limit of viability: Differing perceptions and opinions between neonatal physicians and nurses. *BMC Pediatrics, 18*, 81. doi:10.1186/s12887-018-1040-z

Callister, L. C., & Sudia-Robinson, T. (2011). An overview of ethics in maternal-child nursing. *MCN: The American Journal of Maternal Child Nursing, 36*(3), 154–159. doi:10.1097/NMC.0b013e3182102175

Cavaliere, T. A., Daly, B., Dowling, D., & Montgomery, K. (2011). Moral distress in neonatal intensive care unit RNs. *Advances in Neonatal Care*, *10*(3), 145–156. doi:10.1097/ANC.0b013e3181dd6c48

Coetzee, S. K., & Klopper, H. C. (2010). Compassion fatigue within nursing practice: A concept analysis. *Nursing and Health Sciences, 12*(2), 235–243. doi:10.1111/j.1442-2018.2010.00526.x

Gallagher, K., Marlow, N., Edgley, A., & Porock, D. (2011). The attitudes of neonatal nurses towards extremely preterm infants. *Journal of Advanced Nursing, 68*(8), 1768–1779. doi:10.1111/j.1365-2648.2011.05865.x

Garcia, G. M., & Calvo, J. C. A. (2011). Emotional exhaustion of nursing staff: Influence of emotional annoyance and resilience. *International Nursing Review, 59*(1), 101–107. doi:10.1111/j.1466-7657.2011.00927.x

Garity, J. (2009). Fostering nursing students' use of ethical theory and decision-making models: Teaching strategies. *Learning in Health and Social Care, 8*(2), 114–122. doi:10.1111/j.1473-6861.2009.00223.x

Gibson, K., Hofmeyer, A., & Warland, J. (2018). Nurses providing end-of-life care for infants and their families in the NICU. *Advances in Neonatal Care, 18*(6), 471–479. doi:10.1097/ANC.0000000000000533

Gillam, L., & Sullivan, J. (2011). Ethics at the end of life: Who should make decisions about treatment limitation for young children with life-threatening or life-limiting conditions? *Journal of Paediatrics and Child Health, 47*(9), 594–598. doi:10.1111/j.1440-1754.2011.02177.x

Giuseppe, M., Riccardo, Z., & Del Sordo, S. (2018). Failure of invasive airway placement and correlated severe complications: Dealing with inappropriate training and related medico-legal issues. *Pediatric Critical Care Medicine, 19*(1), 76–79. doi:10.1097/PCC.0000000000001379

Janvier, A., Nadeau, S., Deschenes, M., Couture, E., & Barrington, K. J. (2007). Moral distress in the neonatal intensive care unit: Caregiver's experience. *Journal of Perinatology, 27*, 203–208. doi:10.1038/sj.jp.7211658

Kavanaugh, K., Moro, T. T., & Savage, T. A. (2010). How nurses assist parents regarding life support decisions for extremely premature infants. *Journal of Obstetric and Neonatal Nursing, 39*(2), 147–158. doi:10.1111/j.1552-6909.2010.01105.x

Kuschel, C. A., & Kent, A. (2011). Improved neonatal survival and outcomes at borderline viability brings increasing ethical dilemmas. *Journal of Paediatrics and Child Health, 47*(9), 585–589. doi:10.1111/j.1440-1754.2011.02157.x

Lamiani, G., Dordoni, P., & Argentero, P. (2017). Value congruence and depressive symptoms among critical care clinicians: The mediating role of moral distress. *Stress and Health, 34*(1), 135–142. doi:10.1002/smi.2769

McGibbon, E., Peter, E., & Gallop, R. (2010). An institutional ethnography of nurses' stress. *Qualitative Health Research, 20*(10), 1353–1378. doi:10.1177/1049732310375435

Mercurio, M. R. (2011). The role of a pediatric ethics committee in the newborn intensive care unit. *Journal of Perinatology, 31*, 1–9. doi:10.1038/jp.2010.39

Molloy, J., Evans, M., & Coughlin, K. (2015). Moral distress in the resuscitation of extremely premature infants. *Nursing Ethics, 22*(1), 52–63. doi:10.1177/0969733014523169

Orzalesi, M. (2010). Ethical problems in the care of high risk neonates. *The Journal of Maternal-Fetal and Neonatal Medicine, 23*(S3), 7–10. doi:10.3109/14767058.2010.510647

Pauly, B., Varcoe, C., Storch, J., & Newton, L. (2009). Registered nurses' perceptions of moral distress and ethical climate. *Nursing Ethics, 16*(5), 561–573. doi:10.117/0969733009106649

Peterec, S. M., Bizzarro, M. J., & Mercurio, M. R. (2018). Is extracorporeal membrane oxygenation for a neonate ever ethically obligatory? *The Journal of Pediatrics, 195*, 297–301. doi:10.1016/j.jpeds.2017.11.018

Potter, P., Deshields, T., Divanbeigi, J., Berger, J., Cipriano, D., Norris, L., & Olsen, S. (2010). Compassion fatigue and burnout: Prevalence among oncology nurses. *Clinical Journal of Oncology Nursing, 14*(5), E56–E62. doi:10.1188/10.CION.E56-E62

Richards, C. A., Starks, H., O'Connor, M. R., Bourget, E., Hays, R. M., & Doorenbos, A. Z. (2017). Physicians perceptions of shared decision-making in neonatal and pediatric critical care. *American Journal of Hospice and Palliative Medicine, 35*(4), 669–676. doi:10.1177/1049909117734843

Robichaux, C. (2012). Developing ethical skills: From sensitivity to action. *Critical Care Nurse, 32*(2), 65–72. doi:10.4037/ccn2012929

Rushton, C. H. (2007). Respect in critical care: A foundational ethical principle. *AACN Advanced Care, 18*(2), 149–156. doi:10.4037/15597768-2007-2007

Sano, R., Schiffman, R. F., Shoji, K., & Sawin, K. J. (2018). Negative consequences of providing nursing care in the neonatal intensive care unit. *Nursing Outlook, 66*(6), 576–585. doi:10.1016/j.outlook.2018.08.004

Smith, J. G., Rogowski, J. A., Schoenauer, K. M., & Lake, E. T. (2018). Infants in drug withdrawal: A national description of nurse workload, infant acuity, and parental needs. *The Journal of Perinatal and Neonatal Nursing, 32*(1), 72–79. doi:10.1097/JPN.0000000000000309

Spence, K. (2011). Ethical advocacy based on caring: A model for neonatal and paediatric nurses. *Journal of Paediatrics and Child Health, 47*(2), 642–645. doi:10.1111/j.1440-1754.2011.02178.x

Sudia-Robinson, T. (2011a). Ethical implications of newborn screening, life-limiting conditions, and palliative care. *MCN: The American Journal of Maternal Child Nursing, 36*(3), 188–196. doi:10.1097/NMC.0b013e318210214c

Sudia-Robinson, T. (2011b). Neonatal ethical issues: Viability, advance directives, family centered care. *MCN: The American Journal of Maternal Child Nursing, 36*(3), 180–185. doi:10.1097/NMC.0b013e3182102162

Thorne, S., Konikoff, L., Brown, H., & Albersheim, S. (2018). Navigating the dangerous terrain of moral distress: Understanding response patterns in the NICU. *Qualitative Health Research, 28*(5), 683–701. doi:10.1177/1049732317753585

Ulrich, C. M., & Grady, C. (Eds). (2018). *Moral distress in the health professions*. New York, NY: Springer.

Yoder, E. A. (2010). Compassion fatigue in nurses. *Applied Nursing Research, 23*(4), 191–197. doi:10.1016/j.apnr.2008.09.003

CHAPTER 43

Neonatal Care From a Global Perspective

Carole Kenner and Marina V. Boykova

INTRODUCTION

In 2005, *The Lancet* published the "Neonatal Survival" issue (Lawn, Cousens, & Zupan, 2005). This report called for action worldwide to address the United Nations Millennium Development Goals, especially #4 to reduce mortality of children less than 5 years of age. Why a call for action by perinatal and neonatal specialists who care for children in the first year of life? Why call this edition the Neonatal Survival and not child survival? The reason is that almost 50% of the deaths of children under 5 years of age is attributable to the neonatal period (Lawn et al., 2005). Most of the causes, including infection, intrapartal complications, and prematurity, are preventable (Lawn, Kerber, Enweronu-Laryea, & Cousens, 2010). In 2010, a progress report was released stating that the deaths in this population had been reduced from 4 million annually to 3.6 million (Lawn et al., 2010).

To combat these outcomes, the global community responded by producing an action plan for implementation of strategies that would continue the progress. The World Health Organization (WHO, 2012), specifically the Partnership for Maternal Newborn and Child Health–WHO, led the Child Survival Call to Action. This initiative was in collaboration with UNICEF. Over 700 leaders participated in Washington, DC, in this historic meeting (www.who.int/pmnch/media/news/2012/20120614_childsurvival_call/en/index.html). Over the past decade, one key ingredient in improving health outcomes has been nursing. It is recognized that a strategy is to strengthen the education and training of neonatal and pediatric nurses. The March of Dimes, the Partnership for Maternal, Newborn, and Child Health, Save the Children, and the WHO issued a report in 2012, *Born Too Soon* (Howson, Kinney, & Lawn, 2012). In that report, there is also a call to action citing that, to date, 15 million babies worldwide are born prematurely, with 60% of these births occurring in Africa and South Asia. The United States is in the top 10 countries that are the highest contributors to preterm births (Howson et al., 2012). The call to action lists four shared actions. **Invest:** Ensure preterm interventions and research are given proportional focus, so funding is aligned with health burden. **Implement:** Plan and implement preterm birth strategies at global and country levels and align on a preterm mortality reduction goal. Introduce programs to ensure coverage of evidence-based interventions, particularly to reduce preterm mortality. **Innovate:** Perform research to support both prevention and treatment agendas. Pursue an implementation research agenda to understand how best to scale up interventions. **Inform:** Significantly improve preterm birth reporting by aligning on a consistent definition and more consistently capturing data. Raise awareness of preterm birth at all levels as a central maternal, newborn, and child health issue. The overarching message is continued support for "Every Woman Every Child" and other reproductive, maternal, newborn, and child health efforts, which are inextricably linked with preterm birth. Ensure accountability of stakeholders across all actions (Howson et al., 2012, p. 7). The Every Woman Every Child global strategy continues and the Every Newborn Action Plan is now in the implementation phase (Every Woman Every Child, n.d). This plan provides a roadmap to end preventable neonatal deaths (Every Woman Every Child, n.d.). Endorsed in 2014 by the World Health Assembly, this work now includes a Quality of Care Network, Partnership to Prevent Preterm Birth, and Breastfeeding Advocacy Initiative (Every Woman Every Child, n.d.). At country level, there is now a commitment to track neonatal health outcomes including barriers to providing care (Every Woman Every Child, n.d.).

This work is improving outcomes but not fast enough. According to UNICEF (2018), in 2017 the neonatal mortality rate was 18 per 1,000 live births, which translated to 7,000 deaths daily, and 2.5 million deaths per year. WHO (n.d.-a) cited that in 2016 there were approximately 2.6 million neonatal deaths annually. This constitutes 46% of all under-five deaths. The top 10 countries for neonatal, maternal mortality and stillborn rates are India, Nigeria, Pakistan, China, Democratic Republic of the Congo, Ethiopia, Bangladesh, Indonesia, Afghanistan, and Sudan (Bhutta, 2018). The highest neonatal mortality rates occur in Africa—Somalia, Mali, Democratic Republic of the Congo, Sierra Leone, Central African Republic, Burundi, Angola, and Chad—and two countries outside Africa—Afghanistan and Pakistan (Bhutta, 2018). Preterm birth constitutes about 35% of this mortality (Bhutta, 2018). Most neonatal deaths occur on the first day of life (WHO, n.d.-a). There is much work to be done globally to decrease morbidity and mortality of mothers, neonates, and children. Nurses are key to making a difference. Nursing Now (n.d.) has declared 2020 as the year of the nurse to coincide with Florence Nightingale's 200th birthday. This initiative is supported by WHO and the International Council of Nurses (ICN) to empower nurses (WHO, n.d.-b).

Raising awareness of the factors that contribute to these rates, improved education and training of health professionals and community health workers, and a commitment to raise the standards of maternal–child care are the cornerstones to changing the global picture. To this end, this chapter is dedicated to the efforts that are at work to change neonatal nursing and neonatal and child outcomes. It also presents exemplars of neonatal nursing and its struggles as well as its opportunities.

A STRONG GLOBAL VOICE FOR NEONATAL NURSING

The Council of International Neonatal Nurses (COINN) was founded in 2005 by national neonatal nursing organizations that believed that a strong voice for neonates and their families was essential. These national members felt that already strong organizations needed to work together to help nurses in countries where there were no national organizations. Many times, there were only a few nurses, and obviously they could not be trained or specialized in just neonatal care. These nurses, so few in number, needed to provide care across the life span. The founding groups were the National Association of Neonatal Nurses (NANN) in the United States; the National Neonatal Association (NNA) of the United Kingdom; the Australian College of Neonatal Nurses (ACNN), formerly the Australian Association Neonatal Nurses Association; the New Zealand Association of Neonatal Nurses (NZANN) or Neonatal Nurses College of Aotearoa; and the Canadian Association of Neonatal Nurses (CANN). Over the next 7 years, other national organizations joined, including the Danish Neonatal Nurses, Netherlands Innovation and Research-Dutch NICUs, Finnish Society of Neonatal Nurses-Finland, and Sociedad Española de Enfermeria Neonatal (SEEN), Spain. COINN helped launch organizations in Southern Africa—the Neonatal Nursing Association of Southern Africa (NNASA); India—the Indian Association of Neonatal Nurses (IANN), Rwanda—the Rwanda Neonatal Nurses Association (RANN) in 2016; the Japanese Academy of Neonatal Nurses joined COINN in 2016, the Kenya Neonatal Nurses Association (KNNA) launched in 2018, a network formed in Russia, and COINN is beginning to discuss such work in Burundi, Democratic Republic of Congo, and Brazil. Other areas of the world have offered regional representatives who can link nurses together in their region of the world. Through these efforts, over 70 countries are now represented by COINN. Why is this type of nongovernmental, nonprofit organization important?

COINN'S Role in Global Health

COINN has joined forces with many partners worldwide to address the issues of newborn health standards, neonatal nursing recognition as a specialty, and the need for lifelong learning for those caring for mothers and babies. COINN's partners are the 99nicu Forums, Caring Bridge, European Foundation for the Care of Newborn Infants (EFCNI), the Healthy Newborn Network, as an affiliate of the International Council of Nurses, the Partnership for Maternal Newborn and Child Health–WHO, and the White Ribbon Alliance for Safe Motherhood, to name a few. COINN has issued position statements on the Care of the Late Preterm Infant, Care of the Well Term Infant, Child Health, Poverty and Breastfeeding, Ethical Migration of Neonatal Nurses, Neonatal Nursing Education, and Routine Screening for Intimate Partner Violence. COINN has endorsed documents from other organizations that are helping to shape health policy and standards of care at both national and global levels. From 2017 to 2018, COINN has participated in several high-level United Nations meetings, contributed to the Every Woman Every Child and Every Newborn Action plan by committing to training in Helping Babies Breathe™, Essential Newborn Care, and in partnership with Dr. Kris Karlsen of S.T.A.B.L.E. COINN is working with USAID, WHO, and others on a next round of training and policies to be implemented in 2019. COINN received funding from Chiesi Foundation, Parma, Italy, and Dr. Sue Prullage's leadership from COINN to conduct research to determine skills, knowledge, and staffing issues as well as equipment used in all the neonatal units in Rwanda. Rwanda's outcomes are better than that of their surrounding neighboring countries, yet they have many challenges. In October 2018, COINN held its first regional African Conference in partnership with the University of Rwanda, Training, Support and Access Model (TSAM), Global Engagement Institute (GEI), Berlin, Germany, with an office in Rwanda, and others. This meeting attracted over 300 people—primarily nurses from Rwanda, Kenya, Democratic Republic of Congo, Burundi, Zambia, Malawi, and Nigeria as well as the United States and Australia. At this meeting, a side meeting was held to run focus groups to determine barriers, opportunities, and aspirations of nurses in the African countries. Following the focus groups, thought leaders came together from USAID, WHO, GEI, Chiesi, Save The Children, Partners in Health, BirthLink, Project Hope, Rwanda Midwifery Association, Preterm Birth Initiative of University of California San Francisco (funded by the Gates Foundation), COINN, and RANN to begin to develop a roadmap for improving the visibility of nurses and thereby improving neonatal outcomes. This conference/side meeting was most important as it spoke to nurses' vital role in healthcare. This work, along with the Nursing Now Campaign with WHO and ICN, will help with gender equity issues as nursing is still predominantly a female profession (Nursing Now, n.d.; WHO, n.d.-b). COINN also works with the Joint European Neonatal Societies (JENS) to represent nursing's voice at their conferences. In October 2018, COINN board members Agnes Vanden Hoogen and Julia Petty participated in the eighth International Congress of Union of European Neonatal and Perinatal Societies (UENPS). As was started several years ago with the Every Woman Every Child initiative, bottlenecks to care provision need to be identified and relieved to care for the small and sick newborn (Moxon et al., 2015). Some examples of the global perspective and why many issues are the same worldwide are presented in the next sections.

European Foundation for the Care of Newborns and Infants

The EFCNI was founded in 2008 to address the issues surrounding premature infant birth and the infants' families. Since then, this organization has formed alliances with nongovernmental and governmental organizations, including the March of Dimes, European Parliament, and many others, to promote policy changes in the European Union. COINN has endorsed some of their more recent reports. They have issued several landmark reports and white papers. Their Benchmarking Report of 2010 (EFCNI, 2010) highlighted successful ingredients for changing the prematurity rates and outcomes.

Key factors that determine an effective and successful approach to tackling prematurity include the following:

- National neonatal health policy/program;
- Formal dialogue between government, healthcare professionals, and parents;
- Comprehensive data collection on prevalence/morbidity/mortality/cost burden based on standardized definitions and common measurement criteria (e.g., through registries);
- Comprehensive data collection on neonatal intervention outcomes/neonatal service management based on common measurement criteria (EFCNI, 2010, p. 7).

EFCNI issued a white paper in 2012 on caring for newborns and infants. This white paper is a call to action to address the provision of quality and safe maternal infant care (EFCNI, 2012). Thirteen key recommendations were made. While the focus was on Europe, the reality is that these recommendations fit any country.

The 13 key recommendations made in this white paper identify that action is needed at both the European and national level in order to do the following:

1. Recognize the issues of maternal and newborn care and aftercare as a public health priority, particularly the health of preterm infants and infants with illnesses;
2. Acknowledge the potential long-term health consequences of preterm birth and newborns with illnesses that need to be tackled;
3. Address health inequalities in maternal and newborn care within all EU member states;
4. Conduct national audits on maternal, newborn care, and aftercare services and establish multidisciplinary task forces for developing national best practice guidelines;
5. Implement national policies and guidelines for high-quality preconceptional maternal and newborn care and aftercare. These policies and guidelines should include the principles highlighted in this white paper.
6. Provide equal and early access for parents to complete and accurate information, education, and counseling;
7. Harmonize education and training of healthcare providers;
8. Provide social and financial support for parents and families;
9. Develop and implement strategies for public awareness and education;
10. Harmonize cross-border maternal and newborn healthcare;
11. Monitor outcomes and implement audit procedures in maternal, newborn, and aftercare services;
12. Implement Europe-wide standardized datasets for pregnancy and preterm birth outcomes;
13. Invest in comprehensive research to tackle the challenge of preterm birth and its potential long-term consequences (EFCNI, 2012, pp. 5–6).

In the fall of 2018, the *European Standards of Care for Newborn Health* will be released by EFCNI. COINN worked with EFCNI to develop these standards. This is just another example of health professionals and families working together.

RUSSIAN EXAMPLE

Neonatal nurses in Russia have worked hard to raise the status of nursing in their country. They have a very strong Russian Nurses Association that has been a member of the ICN for almost a decade. This group is working to raise the standards of nursing and supports exchanges with other countries. At the same time, Russian neonatal nurses have formed a network to address the specific care and educational needs of neonates and their caregivers. For example, Children's Hospital #1 in Saint Petersburg developed collaboration in the early 1990s. Neonatal teams went back and forth between Russia and Oakland Children's Hospital, Oakland, California. Through this exchange, infection rates as well as neonatal mortality rates dropped significantly (Kenner, Sugrue, Mubichi, Boykova, & Davidge, 2009). Medical leadership in Saint Petersburg supported neonatal nurses going to England to gain bachelor's and master's degrees. The administration supported a neonatal nurse educator at the unit level. Unfortunately, such efforts were not common in Russia, and some places have even eliminated unit educators. On the positive side, Russia has free follow-up care for mothers and babies, including home visits. This country has also supported changing the role of nurses to a more professional level. In the past, it was not uncommon for nurses to sweep and scrub the floors and empty trash in addition to providing care. This unit in Saint Petersburg is the largest NICU in Europe, with 200 beds. It maintains good outcomes, but nurses today face new challenges of providing care with little orientation or specialized training.

INDIAN EXAMPLE

Indian neonatal nurses and neonatologists recognized that there was a growing problem of sicker, smaller babies requiring care. The Neonatology Forum of India, which represents the doctors, encouraged the neonatal nurses to work together with them and seek help from COINN to form a national organization. In 2007, this call to action resulted in the formation of the Indian Association of Neonatal Nurses. The 2007 COINN International Conference of Neonatal Nurses hosted by the Indian Neonatal Nurses Association brought together over 1,000 nurses and doctors from around the globe. Why was this important? At one session during the conference, the president of COINN and a local neonatologist facilitated a discussion of the state of neonatal nursing in India. There, it was revealed that even though it might be considered a Level II or intermediate care unit, the ratio was 75 babies to 1 nurse. The staffing was at critical levels as the nursing shortage was growing. Nurses were frustrated they could not provide the care they wanted so desperately to give. While, of course, this staffing was not the case everywhere in India, the neonatal outcomes were not good. For example in the *Born Too Soon* report (Howson et al., 2012), India is reported to have had just over 27 million births in 2010, with 13 in 1,000 live births being preterm, resulting in over 875,000 neonatal deaths. These figures are just for premature births and not for other neonatal problems. With the sanction of the Ministry of Women's and Children's Health, the IANN was launched in 2007. Since that time, this organization with COINN has advanced neonatal nursing. *Saving Newborn Lives* in conjunction with COINN gave awards to three nurses to attend the international conference hosted by the NNASA and COINN in Durban, South Africa, in 2010. One of the awardees was from the Indian group. Participating in such conferences and having organizations work collaboratively are making a difference. India still faces many challenges as the neonatal mortality rate continues to be high. Nursing must be a part of the solution. The following sections provide exemplars of work going on globally to change neonatal care and education.

SOUTH AFRICAN EXAMPLE

For many years, the challenge of maternal–child health in sub-Saharan Africa has been highlighted. The highest neonatal death rates worldwide are still found in this region. The rate of premature births in South Africa in 2010 was 8 per 1,000 live births, with total births just over 1 million; neonatal deaths due just to prematurity were over 18,000 (Howson et al., 2012). Neonatal nurses had enjoyed a time when their specialty was recognized by the nursing council; however, as the nursing shortage grew, the need for more generalized training grew. Thus, specialized neonatal training was only supported at an institutional or unit level. The neonatal nurses brought the minister of health and *Saving Newborn Lives* to the international conference with COINN. From that meeting, there were media releases to support the need for more education and training, as well as for nurses working with nongovernmental and governmental agencies to improve neonatal outcomes. Policy

changes are slow, but with this organized voice and now thanks to media coverage and more recognition of the vital role nurses play in improving outcomes, progress is being made (Kenner, Boykova, & Eklund, 2011; Kenner et al., 2009). Educational outreach is growing, as are the requests for neonatal nurses to work at the policy table to change neonatal care. Southern Africa, South Africa in particular, must be viewed within the context of a change in healthcare delivery due to the increasing impact of HIV. As hospitals got overcrowded with patients with HIV/AIDS, South Africa developed community-based programs such as home visits and palliative care (Zelnick, 2011). Need for nurses grew at a time when wages and work conditions grew worse (Zelnick, 2011). Nurses, including neonatal nurses, began migrating to other countries, contributing to the brain drain (Zelnick, 2011). This migration, coupled with the growing needs for generalist nurses, has led to tensions for specialized education, especially in the area of maternal–child outcomes. The situation has not really changed in the past few years. But now, with support from nongovernmental organizations, nursing is increasing its presence in the discussion about ways to change the view of nursing. Most of Southern Africa has better neonatal health outcomes than many other countries. More evidence is needed to determine the role nursing education and training has had on these outcomes.

BRAZILIAN EXAMPLE

In June 2012, the Brazilian neonatal nursing community came together in the second annual *Congresso Brasileiro de Enfermagem Neonatal* meeting, held in Fortaleza, Brazil. Almost 1,000 nurses and doctors were in attendance. Amazing work is going on there. A national repository exists to collect data on maternal–child outcomes. Interprofessional teams are beginning to emerge in the educational institutions as well as the practice arena. The nurses are working with policy makers to ensure that the standards of nursing and care are raised. Brazilian nurses are gaining opportunities for more autonomy in practice. They are viewed by many doctors as the key to changing the outcomes for the country. Prematurity rates have decreased over the past decade, and there is more emphasis being placed on breastfeeding, nutrition, and developmental care. Infectious disease is still a problem, as it is globally. They have formed a national research network that encompasses public health initiatives. Brazil is considered one of the BRIC countries—Brazil, Russia, India, and China. This refers to the growing economies in these countries and the important role they will have in changing global markets. For health, this means that more countries will want to invest in BRIC and therefore will need a healthy workforce to draw workers from and to maintain. According to UNICEF, the younger than 5 years of age mortality rate in 1990 was 59 in 1,000 live births, but by 2010 the rate was 19 in 1,000 live births (UNICEF, 2012a). By 2017 the under 5 years of age mortality rate was 14.8 per 1,000 live births (UNICEF, 2019). The neonatal mortality rate in 2010 was 17 per 1,000 live births (UNICEF, 2012a). Definite progress is being made in this country. This progress demonstrates the impact of improved nutrition, promotion of breastfeeding, increased support for reproductive health efforts, a strong public health model that includes examining differences between risk and poor populations and the factors that contribute to the differences, provision of public safe water, increased awareness of prematurity and rationale for decreasing elective cesarean sections, as well as monies to support vaccinations and treatment for infectious diseases including pneumonia and diarrhea (Holtz, 2013). With the outbreak of the Zika, monies have been allocated for prevention and treatment and nurses are included in this work. Brazil continues to work to decrease premature births through public education about the dangers of prematurity including the dangers of nonessential cesarean sections.

JAPANESE EXAMPLE

Japan is a global economic and technologic force. Yet neonatal nurses in Japan have a limited role. Nurses in Japan oftentimes are not permitted to do any invasive procedures such as start intravenous therapy; they cannot easily question a doctor's authority, nor can they always contribute to the assessment (Kenner et al., 2011). Tides are changing as nurses and doctors are being invited to lecture and work in Japan to raise the awareness of Western techniques and care standards (Kenner et al., 2011). Gradually, policies are changing through these exchanges. Collaborative efforts are under way to gather groups already working in Japan to address common issues such as neonatal care standards rather than working individually (Kenner et al., 2011). The Japan Academy of Neonatal Nursing joined COINN in 2016. They have been a long-standing organization but felt the time was right to join forces with COINN to increase educational/networking opportunities for their nurses.

RWANDAN EXAMPLE

Rwanda is a changing country. Neonatal mortality rates were 29 in 1,000 live births (UNICEF, 2012b). The amazing change is in the younger than 5 years of age mortality rate that moved from 163 in 1,000 live births in 1990 to 91 in 1,000 live births in 2010 (UNICEF, 2012b). By 2017, the rate had dropped to 16.4 per 1,000 live births (Knoema, n.d.). How did this change come about? Over the past two decades, governmental and nongovernmental agencies have worked together to change the tides of health in this country. EOSVISIONS, COINN, RANN, GEI, and One Good Deed worked together with the Rwandan Ministry of Health and the Kigali Health Institute to provide neonatal education, specifically Helping Babies Breathe (https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/helping-babies-survive/Pages/Helping-Babies-Breathe.aspx), from the American Academy of Pediatrics and S.T.A.B.L.E. Program developed by Dr. Kris Karlsen of Park City, Utah (www.stableprogram.com; EOSVISIONS, 2012). This collaboration is new, but represents another step in raising the education of neonatal health providers. The formation of the RANN has facilitated discussions about the barriers and opportunities to provide high-quality care. Partnerships with those organizations working in the country to coordinate efforts is most important to changing outcomes.

These are just some examples of challenges as well as opportunities to impact neonatal nursing care and education. There are other broader issues that are also impacting neonatal nursing.

FUNDING FOR NURSING EDUCATION

A major factor in neonatal nursing care is neonatal nursing education. This education is linked to how a country finances medical and nursing education. Many countries fund medical education under the Department or Ministry of Education. However, nursing education is often funded under the Ministry of Health. Obviously, if a country has poor health outcomes and there is increasing political pressure to improve these outcomes, that country will put more financial resources into the care than into education that is competing for the same dollar (Kenner et al., 2009). Mexico, for example, changed this mode of funding several years ago. Nursing education is now funded under education and not health. This is

one example of a policy initiative that needs to continue to be addressed on a country level. COINN and other organizations are raising the awareness of this issue. COINN and other nurses must be involved in the change. They must tell their stories of what it is like to be on the frontlines.

SUMMARY

Global issues in neonatal nursing care and education are at the forefront of the Millennium Development Goals and the Sustainable Development Goals work. It is critical that nurses continue to see a role in changing standards of care for mothers and babies, raise the educational level of neonatal nurses, and work at policy tables to change public and health policies.

CASE STUDY

A 39-week infant was born in a remote village in Central America. The infant was transported by ambulance to a large metropolitan hospital that has an intensive care unit. The infant was diagnosed with a congenital heart defect that could be repaired with surgery. The only pediatric cardiac surgeon was unavailable as he had been in an accident and recovery was expected to take several weeks. The infant was maintained with oxygen in hopes he could survive until the surgeon was well. Transport of the infant out of the region for medical treatment was not possible. This case is replicated in many parts of the world with small variations on a regular basis.

EVIDENCE-BASED PRACTICE BOX

In 2005, Lawn, Cousens, and Zupan, published *The Lancet "Neonatal Survival Series,"* which stated that over 4 million children younger than 5 years old died annually. By 2010, Lawn et al. (2010) reported this number to have been reduced to 3.6 million. By 2017, UNICEF (2018) noted that 2.5 million die during the neonatal period (UNICEF, 2018).

Several strategies were used to reduce this mortality. For example, Lee et al. (2011) report that, of the 136 million babies born annually worldwide, about 8% require help to breathe, while 814,000 neonatal term infant deaths are due to intrapartum-related events resulting in asphyxia. Therefore, this research team conducted a systematic review of neonatal resuscitation and tactile stimulation and the link to neonatal mortality and morbidity whether in term, preterm, hospital, or home birth situations. GRADE criteria were used to determine mortality rate estimates for the Lives Saved Tool (LiST). A Delphi panel was used for effect size determination when there appears to be low-level evidence to support an intervention that was strongly recommended. The findings were that there were 24 neonatal resuscitation studies involving mortality reports, but none included use of immediate newborn assessment and stimulation as the only interventions. The conclusion following the Delphi panel was that, in healthcare facilities, neonatal resuscitation reduces term intrapartum-related death by as much as 30% but is less effective on preterm infant outcomes. In the community, use of low or no technology resuscitation (basic), immediate newborn assessment, and stimulation also had less dramatic effects than in healthcare institutions with term infants. Further research is needed to examine these practices.

References

Lawn, J. E., Kerber, K., Enweronu-Laryea, C., & Cousens, S. (2010, December). 3.6 million neonatal deaths—what is progressing and what is not?. In *Seminars in Perinatology* (Vol. 34, No. 6, pp. 371–386). Philadelphia, PA: WB Saunders.

Lee, A. C., Cousens, S., Wall, S. N., Niermeyer, S., Darmstadt, G. L., Carlo, W. A., . . . Lawn, J. E. (2011). Neonatal resuscitation and immediate newborn assessment and stimulation for the prevention of neonatal deaths: A systematic review, meta-analysis and Delphi estimation of mortality effect. *BMC Public Health, 11*(Suppl. 3), S12. doi:10.1186/1471-2458-11-S3-S12

United Nations International Children's Emergency Fund (UNICEF). (2018). *Neonatal mortality*. Retrieved from https://data.unicef.org/topic/child-survival/neonatal-mortality/

PARENT VOICES

Crystal Duffy

The anger and frustration from a NICU parent is never personal; always remember it is never about you (the NICU nurse). A parent in the NICU is often navigating through the most traumatic and difficult time in their life. Your job should always be to try and make that journey a little easier for them.

Gigi R. Khonyongwa-Fernandez

"Freefalling without a safety net."
This is what NICU parents who have their babies unexpectedly (what premature birth is expected?) in a foreign country can feel like. It is what I felt like. We may be at an even bigger disadvantage in trying to cope with the daily traumas of the NICU because we do not have the natural support system (i.e., safety net) of family and friends around

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us. We are not just in another state but in another country, and in our case, on another continent. We feel lost, like aliens in an unfamiliar situation in an unfamiliar country and sometimes with an unfamiliar language. Familiar customs and cultural supports that we would typically cling to do not exist. We are terrified and feel unanchored. Nurses need to be in tune to this and be gentle and compassionate by providing some familiarity and consistency to such parents. Try to understand what is important culturally to that NICU family, and either provide it or at least be respectful of it. It is also important to communicate clearly what is going on in a way we understand.

Yamile Jackson, PhD, PE, PMP

I grew up in Bogota, Colombia, in a loving family that believes that nobody should suffer alone. My personal and professional purpose changed the day my son Zachary was born 12 weeks prematurely to save my life. The NICU in Houston, Texas, in 2001 did not have a space for us to stay 24 hours; therefore, night after night, I left Zachary scared and suffering alone while I went home without him.

I poured my newly found maternal instinct, my love for Zachary, my professional experience, and PhD in ergonomics and human factors engineering to make a device to support Zachary and me even when we were not together. I needed to lessen my feelings of impotence and being out of control of this baby that was struggling to survive and was feeling a lot of pain.

When he was 3 weeks old, Zachary survived the deluge of Tropical Storm Allison in Houston when power shut down and his life support equipment stopped working. We kept him alive "by touch" for 9 hours until he was evacuated. My chest and love kept him warm and Larry received a crash course on how to "bag" him to help him breathe. He would switch every half hour with a staff member to give Zachary manual breaths.

Read the Readers Digest article by Peter Michelmore entitled "Blackout" (https://goo.gl/fdJR4R).

In those dark hours, I made a promise to Zachary that his pain and struggle to survive were not going to be in vain, and that I would dedicate my life to share with him my love for traveling, and would support parents to help their babies feel loved, grow, and thrive. My prayer was to be given the opportunity to do it on his behalf and not in his memory.

I was granted my wish. Zachary came home after 5 months in two different NICUs. Since then, I have dedicated my life to engineer solutions that translate evidence into practice and to keep the promise I made to my son.

Babies and mothers around the world share the ability to coregulate. There is a tremendous need to raise awareness and education about the importance of early intervention for proper development of the physical, psychological, sociologic, physiologic, and neurologic systems, and prolonged kangaroo care needs to be implemented in countries around the globe.

My experience in traveling to over 45 countries (20+ with Zachary) and the Internet has allowed me to reach professionals globally to educate about the importance of parents and kangaroo care/skin-to-skin contact for bonding and for the best possible quality of life for a lifetime. All newborns in the world, regardless of gestational age, medical condition, or developmental stage, share the need for being nurtured by loved ones, and kangaroo care can meet this need in every corner of the world. It is an evidence-based practice and works in low- and high-technology settings. At Nurtured by Design, we lead on engineering devices for evidence-based developmental care and safe kangaroo care/skin to skin specifically for hospitals. We call our brand The Zaky, and we founded the International Kangaroo Care Awareness Day on his 10th birthday. We do it all on behalf of Zachary, the healthy teenager that is our CIO (Chief Inspirational Officer).

"A baby is born with a need to be loved – and never outgrows it." —Frank Howard Clark

ONLINE RESOURCES

American Academy of Pediatrics. (n.d.). *Helping babies breathe*. Retrieved from https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/helping-babies-survive/Pages/Helping-Babies-Breathe.aspx

BirthLink. Retrieved from https://birthlink.com

Council of International Neonatal Nurses. Retrieved from http://www.coinnurses.org

Critical Path Institute. (n.d.). *International Neonatal Consortium*. Retrieved from https://c-path.org/programs/inc

European Foundation for the Care of Newborn Infants. Retrieved from https://www.efcni.org

Healthy Newborn Network. (n.d.). *Every newborn*. Retrieved from https://www.healthynewbornnetwork.org/issue/every-newborn

International Paediatric Association. Retrieved from http://www.ipa-world.org

Global Engagement Institute. (n.d.). Contact us. Retrieved from https://www.global-engagement.org/contact/

Partnership for Maternal, Newborn & Child Health. (2018). *2018 Partners' forum*. Retrieved from http://www.who.int/pmnch/about/governance/partnersforum/2018/en

Preterm Birth Initiative. Retrieved from https://www.pretermbirth.ucsf.edu

Project Hope. Retrieved from https://www.projecthope.org

Save the Children's. (n.d.). *Born too soon: Kangaroo mother care saves preterm babies* [Video file]. Retrieved from http://vimeo.com/41435895

Saving Newborn Lives. Retrieved from https://www.savethechildren.org/us/what-we-do/global-programs/health/newborn-health/saving-newborn-babies

The S.T.A.B.L.E. Program. Retrieved from http://www.stableprogram.com

United Nations International Children's Emergency Fund. Retrieved from http://www.unicef.org

United States Agency for International Development. (n.d.). *Maternal and child health*. Retrieved from https://www.usaid.gov/what-we-do/global-health/maternal-and-child-health

World Health Organization. (n.d.). *Maternal, newborn, child and adolescent*. Retrieved from http://www.who.int/maternal_child_adolescent/en

REFERENCES

Bhutta, Z. A. (2018). *Global epidemiology of newborn mortality: What? When? Where? Why?* Retrieved from https://www.healthynewbornnetwork.org/hnn-content/uploads/Global-Newborn-Health.pdf

EOSVISIONS. (2012). *EOS neonatal health programs*. New York, NY: Author.

European Foundation for the Care of Newborn Infants. (2010). *EU Benchmarking report 2009/2010: Too little too late? Why Europe should do more for preterm infants*. Karlsfeld, Germany: Author.

European Foundation for the Care of Newborn Infants. (2012). *Caring for tomorrow: EFCNO white paper on maternal and newborn health and aftercare services*. Karlsfeld, Germany: Author.

European Foundation for the Care of Newborn Infants. (2018). European Standards of Care for Newborn Health. Retrieved from https://newborn-health-standards.org

Every Woman Every Child. (n.d.). *Every Woman Every Child's global strategy for women's, children's and adolescents' health*. Retrieved from http://www.everywomaneverychild.org/global-strategy

Holtz, C. (2013). *Global health care: Issues and policies* (2nd ed.). Burlington, MA: Jones & Bartlett.

Howson, C. P., Kinney, M. V., & Lawn, J. E. (Eds.). (2012). *Born Too Soon: The global action report on preterm birth*. Geneva, Switzerland: World Health Organization.

Kenner, C., Boykova, M., & Eklund, W. (2011). Impact on neonatal nursing globally: Exemplars of how US neonatal/perinatal nurses can get involved. *The Journal of Perinatal and Neonatal Nursing, 25*(2), 119–122. doi:10.1097/JPN.0b013e31821a6d8a

Kenner, C., Sugrue, N., Mubichi, F., Boykova, M., & Davidge, R. (2009). Global infant mortality/morbidity: A clinical issue, a global organizational approach (Review). *Critical Care Nursing Clinics of North America, 21*(1), 1–9. doi:10.1016/j.ccell.2008.09.001

Knoema. (n.d.). Rwanda—Neonatal mortality rate. Retrieved from https://knoema.com/atlas/Rwanda/Neonatal-mortality-rate

Lawn, J. E., Cousens, S., & Zupan, J. (2005). 4 million neonatal deaths: When? Where? Why? (Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, Non-P.H.S.). *Lancet, 365*(9462), 891–900. doi:10.1016/S0140-6736(05)71048-5

Lawn, J. E., Kerber, K., Enweronu-Laryea, C., & Cousens, S. (2010). 3.6 Million neonatal deaths—What is progressing and what is not? (Review). *Seminars in Perinatology, 34*(6), 371–386. doi:10.1053/j.semperi.2010.09.011

Moxon, S. G., Lawn, J. E., Dickson, K. E., Simen-Kapeu, A., Gupta, G., Deorari, A., … Blencowe, H. (2015). Inpatient care of small and sick newborns: A multi-country analysis of health system bottlenecks and potential solutions. *BMC Pregnancy and Childbirth, 15*(Suppl. 2), S7. doi:10.1186/1471-2393-15-S2-S7

Nursing Now. (n.d.). Our aims for 2020. Retrieved from http://www.nursingnow.org/our-aims

United Nations International Children's Emergency Fund. (2012a). Brazil statistics. Retrieved from https://data.unicef.org/country/bra/

United Nations International Children's Emergency Fund. (2012b). Rwanda statistics. New York, NY: UNICEF.

United Nations International Children's Emergency Fund. (2018). United Nations inter-agency group for child mortality estimation (UN IGME) 2018 data. *Neonatal Mortality*. Retrieved from https://data.unicef.org/topic/child-survival/neonatal-mortality

United Nations International Children's Emergency Fund. (2019). *Key demographic indicators*. Retrieved from https://data.unicef.org/country/bra

World Health Organization. (n.d.-a). Neonatal mortality. Retrieved from http://www.who.int/gho/child_health/mortality/neonatal_text/en

World Health Organization. (n.d.-b). Nursing Now campaign. Retrieved from https://www.who.int/hrh/news/2018/nursing_now_campaign/en

Zelnick, J. R. (2011). *Who is nursing them? It is us*. Amityville, NY: Baywood.

CHAPTER 44

Competency-Based Education and Continued Competency

Geralyn Sue Prullage

INTRODUCTION

Healthcare and healthcare expenditures have been a focus for the United States and the international community for years. Healthcare expenditures are linked to patient safety and quality of care. Since the 1990s, quality of care has been linked to nursing competencies. The Pew Health Profession Commission (1995) recommended that all regulated healthcare providers demonstrate competencies in knowledge judgment, technical skills, and interpersonal skills throughout their career. The call for competencies in skills and knowledge for healthcare providers necessitated change in the way education was offered and how to evaluate the education. For years after this report, nursing education struggled with how to measure and instruct in nursing competencies. There was an attempt to generalize competencies to all nursing domains without success. Within individual nursing domains, there are differing competencies, such as competencies for an intensive care neonatal nurse versus the neonatal nurse practitioner. Within governing bodies, there are differing competencies. The National Association of Neonatal Nurses (NANN) requires the neonatal intensive care nurse to certify within a four-competency domain, whereas the neonatal nurse practitioner has a seven-competency domain (NANN, 2015).

Internationally, there are differing governing competencies for neonatal nurses. In the United Kingdom (UK), the National Health Service (NHS) provides care for neonates in specialized units. The specialized units consist of a transitional unit, special care, high dependency care, and intensive care (British Association of Perinatal Medicine [BAPM], 2011). The different levels of care required UK educators to look at the needed competencies of nurses working in each unit. They developed a competency document called the Qualified in Specialty (QIS), which addressed the competencies in each unit. The competencies are separated into seven different domains. The Scottish Nurses Association later adopted the QIS competencies (BAPM, 2012). Other countries have developed neonatal competencies, while some have not addressed the issue.

Nursing has historically demonstrated a commitment to assuring competency that relied on initial licensure, testing, continuing education (CE), codes of ethics, and comprehensive certification programs designed to protect public safety (American Nurses Association [ANA], 2015). In 2014, the ANA (2013) reaffirmed the commitment to competencies by stating that, "the registered nurse is individually responsible and accountable for maintaining professional competence" (p. 3). The Institute of Medicine (IOM, 2015) linked nursing certification to improved competencies and overall improvement in patient outcomes. On a larger scale, the National Academy of Medicine, formerly the IOM, recommended core competencies that affect the health of a country. These core competencies were created to be linked to the Sustainable Development Goals (SDG; Premji & Hatfield, 2016). Nursing competencies are linked to the overall care of a nation. In 1999, the former IOM recommended the implementation of periodic re-examination and relicensure of physicians, nurses, and other healthcare providers based on competencies of knowledge of safety practice (Kohn, Corrigan, & Donaldson, 1999).

In response to the IOM call for re-examination and relicensure, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) issued standards requiring documentation of the clinical competency of all nursing staff (The Joint Commission [TJC], 2017). Hospitals were tasked to develop systems for assessing initial and continuing competence for their nursing staff at a time when downsizing was resulting in the loss of both unit-based educators and clinical nurse specialists (CNS). Particularly affected were critical care units, such as the neonatal intensive care unit (NICU), which were already short staffed and had high nursing turnover rates.

As this movement toward documentation of minimal competencies for hospital nurses was developing, educational institutions were looking at terminal program objectives and the ways in which these might translate into minimal competency statements for graduates. By this time, competency-based education (CBE) had gained acceptance in the nursing education community. Because it offered a potential bridge between education and practice, there was hope that CBE would help close the gap between a new nurse graduate's education for practice and actual practice requirements.

This chapter traces the evolution of the competency movement in healthcare, discusses the advantages and disadvantages of CBE, and describes the impact of the competency movement on neonatal nursing practice and education. The future of competency-based neonatal care is discussed.

DEVELOPMENT OF THE COMPETENCY MOVEMENT

Hospital-based or diploma programs that used an apprentice model to integrate classroom learning and clinical performance dominated the American educational system for nurses until the late 1960s and early 1970s (Chapman, 1999). Subsequently, the growing importance of higher education shifted nursing education from the hospital-based training program to the academic setting and transferred responsibility for the competence of the new graduate nurse from the hospital or employer to the university and its educators (Bechtel, Davidhizar, & Bradshaw, 1999). University-based nursing education gained in popularity and the hospital-based programs began to disappear. Furthermore, the IOM recommended that to address the needs of the growing population, the nursing community should become an important player and that it would begin with obtaining a BSN degree. The recommendation from the IOM was that there should be an 80% increase in BSN nurses by 2020 (IOM, 2010).

As the new paradigm for nursing education evolved, so did an enormous shift in the healthcare arena. Patients in hospitals were sicker, older, and more knowledgeable about the care they received. The gap between the knowledge and skills required nursing students to learn in a supervised academic setting' the setting needed to function safely and independently became increasingly evident. Nurse educators began to develop strategies to address the gaps between knowledge and skills. One focus was to address how nursing educators educated nursing students. Students bridge the gap between knowledge and skills best when the nursing educator provides the knowledge in the classroom and demonstrates the skills in the clinical setting (Ajani & Moez, 2011). A call was made for nursing educators to demonstrate competency by blending knowledge and skills into clinical practice. Therefore, nurse educator competencies were developed in 2013 (National League for Nursing [NLN], n.d.).

With the trend from traditional orientation programs to competency-based programs, we saw a shift in how the gap between education and clinical practice was addressed. Orientation and CE became more competency-based instead of self-reported competencies. Orientation of a new nurse is now unit competency-based, replacing the previous expensive and ineffective orientation programs. A new graduate or new hire nurse now knows what is expected of him or her during the orientation process. The process is organized in a way that the newly hired nurse can attain agreed upon competencies and success on the unit. The steps to orientation became organized, particularly aimed at the newly hired nurse demonstrating competencies along the way. These steps include the following:

- Preparation, which includes specific didactic courses and the choosing of a preceptor
- Incorporation of nurses to participate in rounds, reports, and staff meetings
- Goal-directed preceptorship: The new nurse and the preceptor set goals from simple to difficult tasks and documentation of attaining competency each time
- Feedback from the preceptor and nurse together and head nurse biweekly evolving into weekly and monthly meetings as competencies are attained
- Final step is ongoing support once the orientation program is finished—a "buddy" is assigned to be a mentor and go between for the new nurse (Cline, 2013)

In 2010, the IOM produced a document called *The Future of Nursing: Leading Change, Advancing Health*, which changed the landscape for nursing and competencies. Shortly after the IOM document, the Robert Wood Johnson Foundation (RWJF) along with the AARP initiated the "Future of Nursing: Campaign for Action (Campaign)." These two documents catapulted nursing competencies into the limelight, requiring academia and hospital administrators to evaluate how nurses work, receive training, and continuously train (IOM, 2010). Now, there were clearly defined objectives to ensuring competencies in education and the organization. Faculty and healthcare organizations were now to prioritize the appropriate competencies needed for the newly hired nurse. The Commission on Collegiate Nursing Education and NLN Accrediting Commission provided clear-cut clinical performance competencies for nurses that work in all settings and across all life spans (IOM, 2010).

In 2015, IOM released a new report on the progress of nursing. As in 2010, the IOM recommended nursing residency programs and called for these programs to be developed and funded. The nurse residency program requires nurse educators to prepare nurses with the appropriate competencies and for defined competencies to be in place before the nurse enters residency. The defined competencies would be used to track and evaluate the quality, effectiveness, and impact of the program (Altman, Stith Butler, & Shern, 2015).

The next step after defining competencies was how to assess the effectiveness. Clinical competency assessment (CCA) involves several steps and should include several assessment tools:

- What: Is the ability of a nurse to perform the prescribed task based on clinical skill, knowledge, education, and experience?
- How: Ongoing assessments. Organizations are expected to assess, monitor, maintain, and improve nurses' competencies throughout their career. Competency assessments include peer evaluation, direct observation of practice, and simulation.
- Where: An ongoing process in education and training in all clinical settings where nurses are employed.
- Who: Nurse managers are to maintain the records of nurses' competencies. Assessments can be performed by CNSs, advanced practiced nurses, nurse educators and managers, and preceptors who demonstrate proficiency in the clinical task being assessed (Schub & Heering, 2016).

It was then asked how ongoing nurse competencies are documented and proven on an ongoing basis. Nurse managers are to keep a portfolio for each nurse in the unit. Within these portfolios are the required skills checklist, documentation of cultural competency education, and a list of ongoing CE.

Every state has a professional license board that regulates and provides licensing for nurses. Yet, state boards of nursing have different requirements for nurses to prove their CE. CE is considered one way to demonstrate competencies. Of all 50 states, including Washington, DC, 13 do not have a CE requirement and the remaining 37 require from 5 to 45 Continuing Education Unit (CEU) per renewal period (Lippincott Nursing Center, n.d.).

Continuing education not only fulfills certain state requirements it provides an opportunity for nurses to improve competencies related to practice. Peer reviewed evidence based CE can fill in the knowledge gaps related to competencies (Martin, 2019). When nursing knowledge gaps in the form of CE's are addressed patient outcomes improve (Nassari, 2018). When an organization provides the time and CE's nursing satisfaction improves (Perry, Richter and Beauvais (2018). Nursing satisfaction in their job performance and autonomy resulted in increased competence (Perry, Richter and Beauvais, 2018). CE's play an integral role in helping nurses attain and maintain nursing competencies.

COMPETENCE AND COMPETENCY

What is competence? What is competency? Is there a distinction between the two? Is competence measurable? Benner (1982) defined

nursing competency as the ability to perform a task with desirable outcomes under the varied circumstances of the real world. In her work *From Novice to Expert* (1984), Benner positioned competence at the midpoint of a continuum ranging from novice to advanced beginner, to competent, to proficient, and finally to expert. According to Benner (1984), competent practitioners are consciously able to plan their actions but lack speed. It is interesting to note that the stage of being a "competent" practitioner is not the final one. Two stages (proficient and expert) come after the development of competence. The National Council of State Boards of Nursing (NCSBN, 2012, p. 1) stated that "competence" means the ability of the nurse to integrate knowledge, skills, judgment, and personal attributes to practice safely and ethically in a designated role and setting in accordance with the scope of nursing practice.

In its "Position Statement on Professional Role Competence," the ANA (2008) maintains that "an individual who demonstrates 'competence' is performing successfully at an expected level" (p. 3). The ANA further states that "competency is an expected level of performance that integrates knowledge, skills, abilities, and judgment" (p. 3). In 2014, the ANA reaffirmed the previous definition of professional role competency (ANA, 2014). The International Council of Nurses (ICN) describes competence this way: "The practice and competence of an individual nurse within the legal scope of practice is influenced by a variety of factors including education, experience, expertise and interests as well as the context of practice" (International Council of Nurses [ICN], 2013, p. 2).

The terms are interconnected but are not necessarily interchangeable. Levine and Johnson (2012) stated there is no universal definition of competence or a consistent method across domains to measure competence. Each certification body and nursing organization defines its individual competencies. Competency measurement generally consists of a nurse exhibiting an ability to perform a task or how to perform in a defined setting. Typical measurement of competency consists of a skills checklist and the nurse's ability to move well through a simulation at a skills station. Not only is it difficult to document competency, the nursing profession is struggling with how to demonstrate ongoing nursing competencies. Yearly skills laboratories and review of the initial skills checklist to assess for improvement is a poor way to validate a nurse's nursing competency. Levine and Johnson (2012) suggested that competency assessment should take place in four domains:

1. What a nurse "knows" measured by demonstration of known knowledge (example: tests)
2. The nurse's "know-how" based on exhibited competencies (example: skills checklist or in skills laboratory)
3. The nurse "shows how" by demonstrating competency in performance (example: simulation)
4. What the nurse "does" based on action (example: direct observation of practice or scenario simulation)

Based on demonstration of competencies in the four realms, the nurse and organization have a viable way to document present and ongoing competencies.

The terminology moves from demonstrating competence to demonstration of competency-based practice or it is sometimes called competency-based learning. Defining competency-based learning is difficult due to the differing terminology utilized by different educational institutions. Some of the most common synonyms are proficiency-based, mastery-based, outcome-based, performance-based, and standard-based education, instruction, or learning (Great School Partnership, 2015).

Bernikova (2017) examined the education shift from learning to practice orientation outcomes. Within the shift the nurse learns to solve clinical problems based on their cognitive, communicative, organizational and moral experiences. By shifting the dynamics from demonstrating competence to practicing competence within the nurse's practice, it is now definable, measurable, and can be evaluated. Competency is also situational and dynamic, and now the context determines the competencies necessary to perform the job (ANA, 2018). With competency-based practice, the nurse is demonstrating the competence at an expected level that integrates knowledge, skills, ability, and judgment. To continue to function within a competency-based practice, the nurse must engage in lifelong learning, continuously reassess his or her competencies, and be able to identify the gaps in knowledge and skills required to function. With identification of the gaps in knowledge, the nurse is expected to seek integrative learning experiences.

The new graduate nurse or the experienced nurse who is changing practice areas cannot reasonably be expected to be competent at the onset of employment in an acute care environment such as the NICU. It is reasonable to expect, however, that both will acquire initial and ongoing competency if provided with appropriate orientation and opportunities for CE. As the professional organization for neonatal nurses and nurse practitioners (NPs), the NANN, and the National Association of Neonatal Nurse Practitioners (NANNP), a division of NANN, hold responsibility for setting the national standard for initial and continued competence for practitioners in the neonatal population focus. To this end, NANNP published a position statement in 2015, "Standard for Maintaining the Competence of Neonatal Nurse Practitioners," which included recommendations for evaluation and documentation of continued competence for neonatal nurse practitioner (NNP) practice:

- Orientation of the novice NNP should provide several assessment points, utilizing multiple evaluative tools and methods, throughout the period of orientation.
- Evaluation of the experienced NNP should be based on the seven NNP domains and core competencies of NNP practice and should be conducted at least annually.
- Continuing review of NNP competencies and observations of procedures may include either a minimum number of actual procedures or procedural review and simulation (NANNP, 2014).
- A professional portfolio should be developed by both novice and experienced NNPs to provide evidence of individual learning and experience.
- State boards of nursing should request that ongoing competencies be part of the annual evaluation process (NANN, 2015).

The American Association of Nurse Practitioners (AANP, 2013) and the IOM (2010) recommend that for nurse practitioners to be competent, they must commit to and demonstrate continuously their commitment to lifelong learning and professional self-development to ensure quality improvement and safe patient care.

COMPETENCY-BASED EDUCATION (CBE)

What is CBE? CBE has been described in deferring terms such as problem-based learning, mastery-based learning, outcome-based learning, and performance-based learning. The ambiguous terminology creates confusion regarding CBE. In the last 10 years, a movement has been created to clearly define CBE. The U.S. Department of Education (2017) stated that, "Competency-based strategies provide flexibility in the way that credit can be earned or awarded, and provide students with personalized learning opportunities" (p. 1). Competency-based programs are different from traditional education programs, which require a student to meet certain set hours in a classroom. Competency-based programs give

credit for prior learning and look at the learning that the student has done outside of the scope of the actual course regardless of where, when, or how the prior learning was attained. CBE is now about feedback from mastered skills and empowers the student to take responsibility for attaining the skills needed. Feedback is quick and frequent and is given in a structured assessment. Now, feedback is an ongoing learning experience rather than an end result. Educational institutions, individual neonatal units, and certification bodies set the competencies needed to prove mastery of a skill and education (EDUCAUSE, 2014).

Not all educational institutions are utilizing CBE to instruct students. The difficulty is defining the measurable learning objectives when a student moves along the educational process at different paces. The typical way of validation learning was the demonstration of passing a class and obtaining a certain amount of credit hours. Many institutions are struggling to redefine CBE models within already existing student learning management. Institutions of learning must agree on core competencies in order for CBE to be a common method of education (EDUCAUSE, 2014). If CBE is to be a valid way of education, higher education institutions must look at the current educational model and develop a workable framework for their institution. With an increasing emphasis on skills acquisitions and transfer of knowledge, students will need to demonstrate CBE through work experience. Now, higher institutions will need to pay close attention to mentors, coaches, and possible tutors who will be helping the students achieve their competencies. Education will need to move from traditional lectures in classrooms to include internships and project-based activities to validate the competencies (EDUCAUSE, 2014). Based on research, students that have graduated from CBE demonstrate a uniform standard of learning (EDUCAUSE, 2014).

In 2011, over 100 educators came together to define what CBE should include. Based on the recommendation of this panel, quality CBE should include the following:

- Advancement for students that demonstrate mastery of a task
- The competencies they master should be explicit, measurable, and demonstrate transfer of learning that demonstrates student success
- The ongoing assessment should be meaningful and a positive experience for students
- The outcomes should highlight competencies that include application, knowledge acquisition, and development of appropriate skills (CompetencyWorks, 2017).

Nursing competencies may be divided into core and population-focused competencies. Core competencies are the skills and knowledge required for the minimum safe level of nursing performance. Population-focused competencies are the skills and knowledge required for the minimum safe level of nursing care for a specific patient population.

Although some competencies are mandated by accreditation agencies such as TJC, most nursing competencies are derived from standards of practice developed by professional nursing organizations. The National CNS Competency Task Force (2010) has developed and validated core competencies for CNS that are comprehensive, entry-level competencies expected for newly graduated CNS. CNS core competencies include Direct Care, Consultation, Systems Leadership, Collaboration, Coaching, Research, Ethical Decision Making, Moral Agency, and Advocacy. These competencies reflect CNS practice across all specialties, populations, and settings (National CNS Competency Task Force, 2010).

The National Organization of Nurse Practitioner Faculties (NONPF) has developed both core and population-focused nursing competencies for NPs. The most recent version of the "Nurse Practitioner Core Competencies" was published by NONPF in 2017. The competencies have been revised several times and now include the recommendation for educational needs of Doctor of Nursing Practice and NP practice (NONPF, 2017); to build upon previous work that identified knowledge and skills essential to DNP competencies (American Association of Colleges of Nursing [AACN], 2006); and to maintain consistency with the recommendations of the IOM report on "The Future of Nursing" (IOM, 2010). The core competencies include Scientific Foundation, Leadership, Quality, Practice Inquiry, Technology and Information Literacy, Policy, Health Delivery System, Ethics, and Independent Practice (NONPF, 2017). The nine core competencies are expected outcomes for an NP graduate, regardless of population focus, and are "acquired through mentored patient care experiences with emphasis on independent and interprofessional practice; analytic skills for evaluating and providing evidence-based, patient-centered care across settings; and advanced knowledge of the health care delivery system" (NONPF, 2017).

The core competencies can be adapted to fit specific population foci within nursing. NONPF recently established the 2013 Population-Focused Competencies Task Force to adapt the core competencies to each NP population focus that is recognized by the "Consensus Model for APRN Regulation: Licensure, Accreditation, Certification and Education" (APRN Consensus Work Group & the National Council of State Boards of Nursing APRN Advisory Committee, 2008). These NP population foci include Family, Adult-Gerontology, Neonatal, Pediatrics, Women's Health, and Psychiatric Mental Health. The adult-gerontology and primary care NP practices have further competency distinctions (NONPF, 2016). Organizations that are specific to each population focus, such as NANN and NANNP, have a multifaceted role in the development of their own specialized nursing competencies. Such organizations are responsible for developing specific educational standards and clinical guidelines on which professional nursing practice is based. Accordingly, NANN published the "Education Standards and Curriculum Guidelines for Neonatal Nurse Practitioner Programs" in 2014. The Education Standards and Curriculum Guidelines provide a framework on which new NNP programs may be developed and evaluated, as well as a self-study tool for existing NNP programs. Professional nursing organizations are also responsible for monitoring issues that affect the practice of nursing, such as the development of an appropriate healthcare policy, and for supporting research to link nursing interventions to patient outcomes. Finally, they support individual competence by providing educational opportunities for nurses to maintain their skills and knowledge, by influencing changes in state nurse practice acts, and by participating in the credentialing process as appropriate (Matthews, 2012).

Since 2010 and the IOM report about 2020 educational competencies, any organization that certifies advanced practice nurses should have developed educational competencies. The NLN has developed an educational model that encompasses seven core values: caring, diversity, ethics, excellence, holism, integrity, and patient centeredness. The model speaks to competencies from a practical nurse to a doctoral prepared nurse. In 2016, the Commission of Nursing Education Accreditation (CNEA) adopted the NLN educational model to set the standards for nursing education (NLN, 2016). Now the NLN Commission for CNEA collaborate through an accreditation process to promote quality and reliability in nursing education worldwide (NLN, 2016). The accreditation process used the NLN core values of caring, diversity, integrity, and excellence (NLN, 2016). Based on the core values, a set of standards of evaluation has been developed. The standards of evaluation are to be utilized by the faculty and staff that educate

nurses with frequent outcomes evaluation, plans for improvement, and plans of dissemination. Now individual programs have a working core value and standard of evaluation for the individual training programs.

In individual programs and hospital orientation, the core competencies are modeled after the IOM and RWJF. The Quality and Safety Education for Nurses (QSEN) developed core competencies: evidence-based practice, informatics, patient-centered care, quality improvement and safety, teamwork, and collaboration. Burke, Johnson, Sites, and Barnsteiner (2017) performed research on the eight competencies and demonstrated that all eight competencies could be used to assess a nurse's abilities as shown in Table 44.1.

Most professional organizations and national certifying bodies for NPs require a minimum number of hours spent in didactic education, clinical education, or both. Validation of competency versus completion of a defined minimum number of required hours for certification within a population focus continues to be a topic of conversation and controversy among nursing leaders.

Ensuring the competency of new nursing staff requires an organized approach to orientation of the unit and a system of verification and validation of knowledge and skills. Competency-based orientation (CBO) is one form of CBE and is the preferred model for orientation in many institutions because it allows for the variation in nurses' backgrounds. CBO requires a new nurse to continually assess his or her learned knowledge and skills, identifies the need for additional comprehension and expertise, and ultimately cultivates a culture of lifelong learning (ANA, 2018). Ideally, this type of orientation would be an extension of a generic, competency-based curriculum followed by the academic institutions, adapted to fit the clinical or practice setting. CBOs are advantageous for the new hire and the preceptors. The defined competencies give a clear guideline of expectations. The preceptors now can identify more quickly those new hires that are not going to meet the required competencies to work within the unit. The preceptor can guide the next step within the orientation by utilizing the competency verification form and help the orientee address deficit or problematic areas (Swilhart, 2010).

CBO has many advantages. One major advantage is the shortened orientation for experienced nurses (Franquis & Seckman, 2016). In the current economic environment, this can result in significant savings for the unit and the institution. Other advantages include (1) advances in clinical competencies, (2) more confidence, (3) improved work satisfaction, (4) reduction in error rates, and (5) decrease in patient safety events (Franquis & Seckman, 2016). In CBO and nursing residency, the nurse is the driver of his or her orientations with the preceptors serving as expert role models and facilitating the learning of the orientee.

Now that defined nursing education and clinical practice competencies have been developed, what remains to be seen is how the competencies will improve patient safety and quality of care.

IMPLICATIONS FOR NEONATAL NURSING

Because neonatal nursing is a population-focused area of practice, most graduate nurses complete their basic nursing education with little or no clinical experience in the NICU. This places the burden of developing practice competence on the unit and the hospital. As a result of the projected nursing shortage, many NICUs will be employing new graduate nurses at a time when the supply of

TABLE 44.1

EIGHT CORE COMPETENCIES FOR NURSES

Competency Domain	Definition
Continuous quality improvement	Utilizes data and quality improvement methods to identify potential and actual problems and opportunities to provide care that is safe, timely, efficient, effective, and equitable
Evidence-based practice and research	Evaluates and integrates the best current evidence with clinical expertise and patient and family preferences and values for delivery of optimal healthcare and systems effectiveness
Leadership	Effectively collaborates and applies innovative systems thinking to engage in systematic evidence-based problem-solving and decision making to promote effective changes within a complex care delivery system, supporting the vision of the organization
Patient- and family-centered care	Recognizes the patient or the patient's designated person as the source of control and full partner in providing compassionate and coordinated care based on respect for the patients, preferences, values, and needs
Professionalism	Demonstrates a commitment to the nursing profession through lifelong learning adherence to the ANA's Code of Ethics for Nurses, participation in a professional organization, and advancement of community outreach
Safety	Minimizes the risk of harm to patients, families, providers, and self through system effectiveness and individual performance
Teamwork	Effectively engages in the process of cooperation, coordination, and collaboration in an effort to provide safer, high-quality outcomes for patients within inter- and intraprofessional teams, including virtual teams
Technology and informatics	Utilizes appropriate information and technology to communicate, manage knowledge, mitigate error, and support decision making across the continuum

seasoned neonatal nurses is dwindling. The traditional orientation approach of classroom learning followed by a period of joint clinical practice with an assigned preceptor may not be possible. As the competition for new graduate nurses intensifies, many hospitals are developing internship or externship programs.

Internships and externships for the new graduate nurse are a viable option for NICUs. Most newly graduated nurses recognize the paucity of their knowledge and skills for intensive care units and want some type of formalized educational program to become staff nurses in these areas. Depending on the availability of staff development instructors and experienced nurses willing to assume preceptor responsibilities, many internship and externship programs offer a mix of traditional classroom teaching and CBE. To maximize resources, hospitals often combine nurse interns and externs for the classroom work. For example, a large tertiary hospital may offer a maternal–child nursing option, whereas a children's hospital may offer a critical care option. In the former case, the interns and externs may take classes together on maternity and pediatric nursing. In the latter case, the interns may be in class for the critical care core content.

CBE is also well suited to orientation for new graduate nurses and for experienced nurses who are changing their focus area. For the seasoned staff nurse who switches from adult intensive care, the orientation can focus on the neonatal-specific aspects of critical care. The orientation program for this nurse can be individualized to allow credit for knowledge and skills previously learned. An experienced staff nurse who switches from the well-baby nursery to the NICU will need focused education on the critical care aspects of newborns, because he or she already has a knowledge base about concerns common to well and critically ill newborns, such as thermoregulation and hypoglycemia.

Orientation of new graduates to the role of the NNP presents its own set of challenges. As the baccalaureate to DNP educational pathway becomes more common, there will be an increasing number of newly graduated NNPs with very little NICU experience. Even experienced NNPs are responsible for maintaining validation of required competencies. In 2014, the National Association of Neonatal Nurse Practitioners [NANNP] redefined the *Competencies and Orientation Toolkit for Neonatal Nurse Practitioners*. In the second edition, they added identified core competencies and roles, standardized method of validation and measurement of competencies, incorporated neonatal competencies developed by the NONPF, and an updated skills checklist.

The goal of this second edition toolkit is to establish clarity and consistent expectations concerning competencies for NNPs at varying levels, from novice to expert, and to provide a method of evaluating their competence. Ultimately, the intention is to assure the public that the NNP possesses the knowledge, skill, and clinical judgment required for providing safe, effective care (NANNP, 2014). The basic skills needed for NNPs include intubation, umbilical line placement, and chest tube placement. In addition to basic skills needed for NNPs, they may be responsible for performing lumbar punctures, bladder taps, arterial line placement, PICC line placement, intraosseous line placement, circumcision, and participate in an exchange transfusion (NANNP, 2014).

COMPETENCY VALIDATION

With the public and healthcare organizations requiring that a nurse perform safely with the appropriate competency, there has been a greater emphasis on validation of those competencies. Validation of competencies has been redefined and is specific in nature. To validate a nurse's competency, the organization must now demonstrate that the nurse has the knowledge consistent with the science and preparation needed for the specific competency. Not only does knowledge need to be documented, but there must also be documentation that the nurse accurately and consistently performs competently in practice. Tools of validity documentation have undergone vigorous validity and reliability testing. The individual that evaluates a nurse's competency must be specially trained in evaluation and be consistent from nurse to nurse. Documentation of competencies now depends on a well-trained evaluator. No longer is a nurse able to just say that he or she is competent in knowledge and skills. All competencies are now documented on a valid reliable scale and observed by a trained evaluator (Dickerson & Chappell, 2016).

The frequency of validation may vary according to the specific skill. The interval for validation of such skills as neonatal resuscitation is determined by the national standard, as set by the Neonatal Resuscitation Program (Wyckoff et al., 2015). Other skills are usually validated annually or as required by accreditation criteria set forth by TJC. Although there is little written regarding the number of procedures required for an NNP to obtain and maintain competence, the types and number of procedures done by an NNP depend on the practice site and patient population. While variations among practice sites may make achieving and maintaining skill competency a challenge, it is vitally important that NNPs maintain competence in certain procedures. NANNP (2014) recommends the following guidelines for maintaining procedural competence: basic procedural and clinical reasoning skills for neonatal resuscitation, including endotracheal intubation, umbilical catheter placement, and needle thoracotomy, must be mandatory for all NNPs; maintenance of a procedural skills log documenting procedures performed, including success rates and complications, should be reviewed as part of an NNP's annual evaluation; and education and evaluation of competence for any procedure should be standardized to include use of universal precautions, use of the time-out, review and discussion of informed consent issues, procedural review, and assessment and management of the infant's comfort and pain. Minimal competence should be defined as performing a preset number of procedures defined by the employing hospital and accrediating body.

Competency validation can be achieved through a variety of mechanisms, including chart or record review, simulation, 360-degree evaluation, portfolio, procedure or case logs, or patient survey (NANNP, 2014). For many skills, a combination of methods is used. For example, the validation of neonatal resuscitation skills includes objective examinations and simulation performance evaluations. TJC stresses that competency validation should be obtained from past and current employers, peer evaluation, obtaining of specialty certifications, testing of competencies, current performance evaluations, and observed skills by a trained competency tester (TJC, 2016).

CONTINUING COMPETENCE

According to the ANA (2014), assurance of continued competence is the shared responsibility of the profession, individual nurses, professional organizations, credentialing and certification entities, regulatory agencies, employers, and other key stakeholders. Maintaining individual competence is the professional obligation of every neonatal nurse. This obligation is spelled out clearly and reaffirmed by the ANA in its position statement on *Professional Role Competence* (ANA, 2014): "The public has a right to expect registered nurses to demonstrate professional competence throughout their careers. ANA believes the registered nurse is individually responsible and accountable for maintaining professional competence" (p. 1).

Certification is a process that functions on a continuum throughout a nurse's career that is supported by *lifelong* learning

and ongoing professional development. Voluntary certification is an excellent mechanism for staff nurses, CNS, and NPs to document their ongoing competence in neonatal nursing. In addition to measuring knowledge that is unique to a specific population, national certification examinations require documentation of ongoing education to maintain the certified nurse's expertise. Examinations for neonatal critical care nurses and specialists are available through the American Association of Critical-Care Nurses (AACN) Certification Corporation (AACN, 2017). The National Certification Corporation (NCC) offers several examinations for neonatal nurses. These include examinations for both neonatal intensive care nursing and low-risk neonatal nursing care. Subspecialty areas, such as electronic fetal monitoring and neonatal pediatric transport, are also available to certified nurses (NCC, 2019). In recognition of the expanding knowledge base needed to function in an increasingly complex healthcare environment, the NCC replaced their Certification Maintenance Program with Continuing Competency Initiative (NCC, 2019). The focus of the new program is to determine that each certified nurse has maintained knowledge of the core competencies related to the certification specialty role. A specialty assessment evaluation is being utilized to identify targeted individual-specific CE needs to address knowledge gaps and provide a learning plan that the certified nurse can follow to meet certification maintenance requirements (NCC, 2019). NCC notes that this approach "brings greater accountability and transparency to the certification maintenance process while providing employers and the public a valid measure of assurance regarding the ongoing competency of nurses certified by NCC" (NCC, 2019).

INTERNATIONAL NEONATAL NURSING COMPETENCIES

After the accomplishments of the Millennium Development Goals (MDG) in 2015, the World Health Organization (WHO) moved to Sustainable Development Goals (SDG) to ensure continued improvement in the care of the world population. Specific to neonatal care is the SDG 3.2, which states every country should work to decrease the neonatal mortality rate to 12 deaths per 1,000 live births (WHO, n.d.-b). The neonatal period is the most vulnerable time for a child's survival. In 2016, it was estimated that 7,000 newborns died each day (WHO, n.d.-a). If the current trends continue, over 60 countries will miss the SDG 3.2 goal, and these countries will carry 80% of the burden of neonatal deaths (WHO, n.d.-a). Several strategies have been employed to ensure that these countries achieve SDG 3.2 or decrease their neonatal mortality rate. One of the strategies is to look at neonatal nursing and the accompanying competencies. Neonatal nursing education is currently being added to university-level courses in many countries with the highest burden rate. Training in resuscitation is mandated by many countries. There has been a call to look at and develop neonatal nursing competencies in the high-burdened countries.

In 2017, the Council of International Neonatal Nurses performed a survey with 5,000 members. Six key questions were asked: (1) Does your country have any officially accepted and applied neonatal nursing competencies? (2) Who is responsible for writing and publishing neonatal nursing competencies in your country? (3) Do you think neonatal nursing competencies are needed in your country? (4) Would you like to help develop neonatal nursing competencies for your country? (5) How many years have you worked in a neonatal unit? (6) Which continent do you live in? The results of this study are illustrated in Figures 44.1 to 44.6. Although the percentage of the answers came from North America and Africa, it is obvious there was a great deal of interest in creating neonatal competencies for their counties and a willingness to volunteer to work on the document. The call to decrease neonatal mortality is compelling, and neonatal nurses can be at the forefront of this movement. Developing neonatal competencies and the ongoing validation process will be needed.

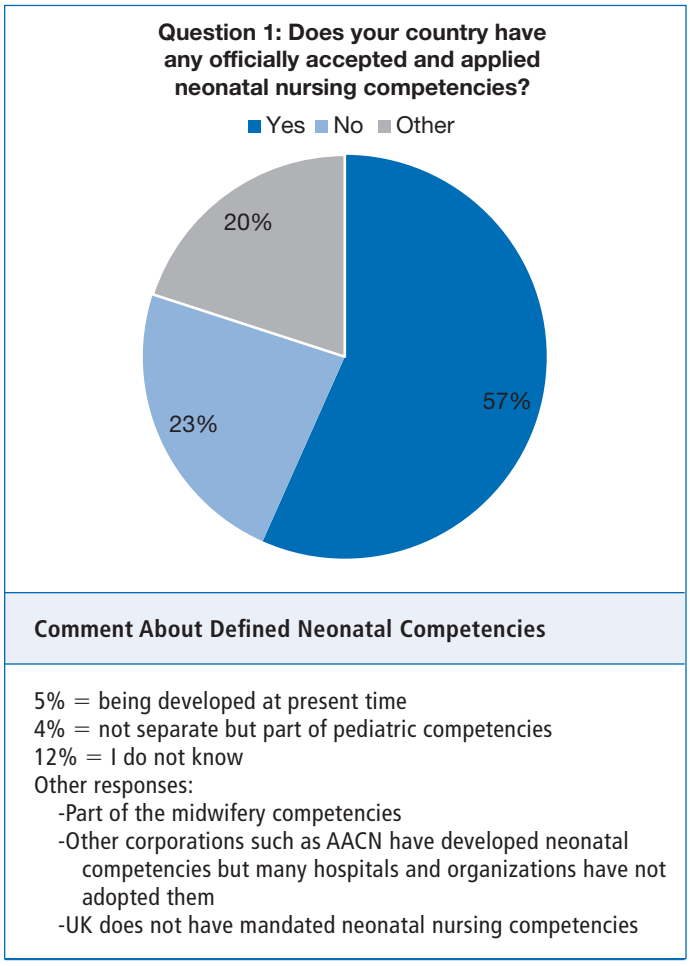

FIGURE 44.1 Results of Council of International Neonatal Nurses survey: Officially accepted and defined neonatal competencies.

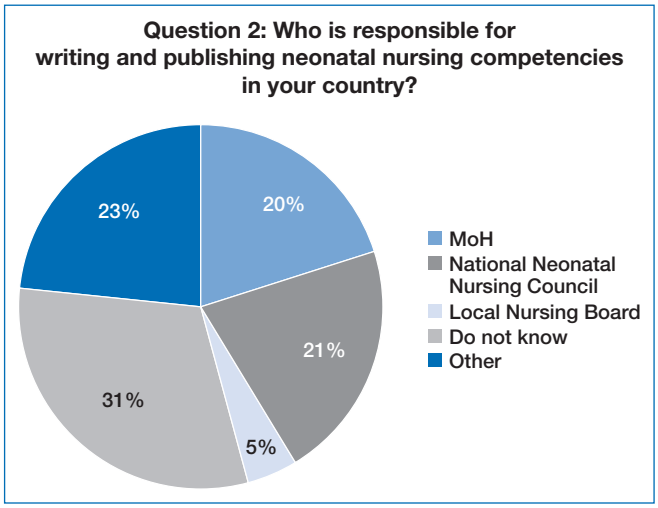

FIGURE 44.2 Results of Council of International Neonatal Nurses survey: Who is responsible for writing neonatal nursing competencies?

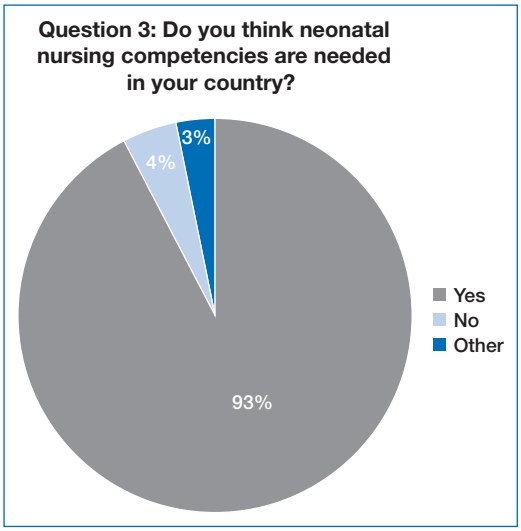

FIGURE 44.3 Results of Council of International Neonatal Nurses survey: Believe neonatal competencies are needed.

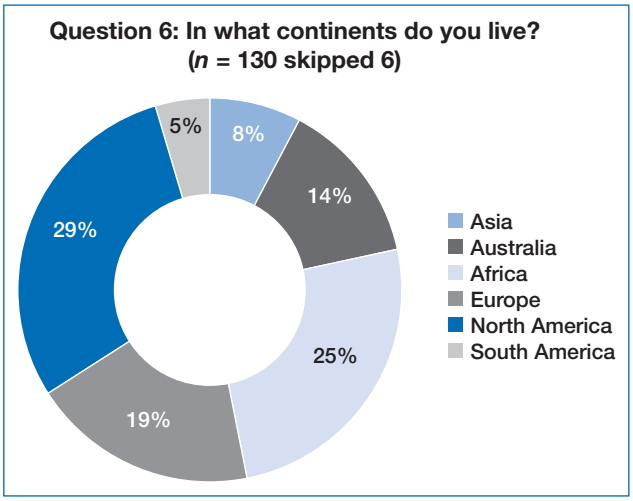

FIGURE 44.6 Results of Council of International Neonatal Nurses survey: What continent do you live in?

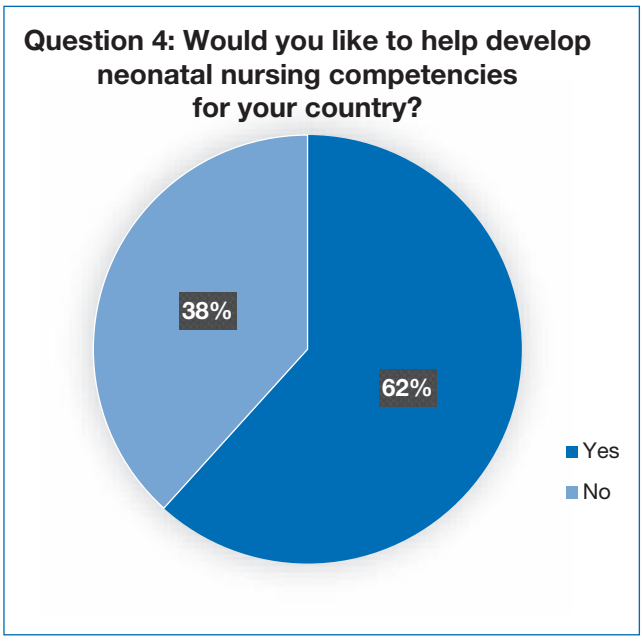

FIGURE 44.4. Results of Council of International Neonatal Nurses survey: Would you like to help develop neonatal competencies for your country?

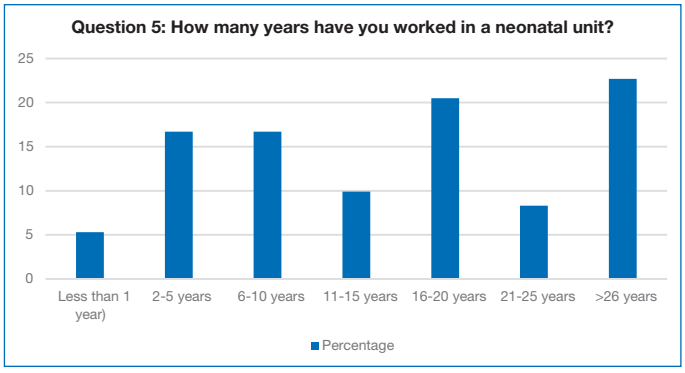

FIGURE 44.5 Results of Council of International Neonatal Nurses survey: How many years have you worked in a neonatal unit?

SUMMARY

Ensuring the competency of neonatal nurses and advanced practice nurses is a major concern of hospitals, regulators, insurance companies, and the public. Changes in the healthcare industry as a result of managed care, mergers of provider institutions such as hospitals, and significant reorganization within the delivery system have placed new demands on the nursing profession to ensure the ongoing competence of its members. Individually and collectively, nurses are challenged by the need to keep current in the midst of a knowledge and technology explosion, by the demand from payers for greater productivity and efficiency in healthcare, and by consumers' growing sophistication regarding the consequences brought about by incompetent providers. Standards of nursing practice and accreditation criteria from professional nursing organizations and agencies such as TJC are used to develop nursing competencies.

CBE provides a mechanism for contemporary nursing to provide a cost-effective, quality approach to nursing education. The competency-based approach is also well suited to individualizing orientation programs to meet the unique needs of nurses who have significantly different backgrounds and levels of experience. CBE shifts the focus of learning from the traditional model of objectives and classroom teaching to a new model based on achievement of specified competencies and outcomes.

Validation of competence is essential to ensure that the nurse continues to maintain the level of expertise necessary to provide safe, effective, quality care. A variety of methods and evaluative tools are currently used to validate nursing knowledge, and skills may include direct observation, patient records, portfolio, demonstrations, skills laboratories, certification, credentialing, simulation exercises, virtual reality testing, targeted CE with outcomes measurement, employer skills validation, and practice evaluation. While there is a variety of methods available, no single tool or method can guarantee competence.

Assurance of continued competence is the shared responsibility of the profession, professional organizations, credentialing and certification entities, regulatory agencies, employers, and other key stakeholders. Ultimately, however, maintaining competence is the professional obligation of each individual nurse. Continued competence is an ongoing process throughout

a nurse's career that must be supported by lifelong learning and ongoing professional development. Each nurse is individually responsible and accountable for maintaining professional competence.

Internationally, nurses who work in neonatal units are interested in developing neonatal competencies and validation. Perhaps the pool of neonatal nurses could be utilized to develop an international competency statement that could be utilized to help hospitals, educational institutions, and political stakeholders develop competencies specific for their countries and institutions. The development of neonatal competencies can pave the way for high-burden countries to achieve SDG 3.2.

EVIDENCE-BASED PRACTICE BOX

Nursing is a complex combination of theory and practice that must be successfully integrated by nursing students in order for them to attain competence. Competence assessment methods must therefore be capable of measuring both knowledge and skills. The portfolio has been identified as a valuable means of assessment, enabling students to demonstrate achievement of competencies by presenting evidence from a variety of sources that display their experience, strengths, abilities, and skills. Hwang, Kuo, and Tu (2017) validated a health education competency tool for nursing students and practicing nurses. The tool consisted of 33 questions in four domains: planning (8 items), pedagogy (15 items), empowerment (6 items), and motivating discourse (4 items). Planning questions consisted of assessment, design, and evaluation. Pedagogy included didactic skills, evidence-based knowledge, and organized teaching content. Motivating discourses included dissonance, appreciate belief system, roll with resistance, grasp client perspective, affirm client efforts, and collaborate to evocate plan. Empowering consisted of support of autonomy and establishing relationship. The tool demonstrated high reliability and validity.

Reference

Hwang, H. L., Kuo, M. L., & Tu, C. T. (2017). Health education and competency scale: Development and testing. *Journal of Clinical Nursing, 27*(3–4), e658–e667. doi:10.1111/jocn.14116

ONLINE RESOURCES

American Association of Colleges of Nursing. (2011).*Core competencies for interprofessional collaborative practice*. Retrieved from: https://www.aacom.org/docs/default-source/insideome/ccrpt05-10-11.pdf?sfvrsn=77937f972

Gruppen, L. D., Mangrulkar, R. S., & Kolars, J. C. (2012). The promise of competency-based education in the health professions for improving global health. *Human Resources for Health, 10*, 43. doi:10.1186/1478-4491-10-43

Health Professionals for a New Century: Transforming Education to Strengthen Health Systems in an Interdependent World. Retrieved from http://www.healthprofessionals21.org

National Organization of Nurse Practitioner Faculties. Competencies for Nurse Practitioners. Retrieved from http://www.nonpf.com/displaycommon.cfm?an=1&subarticlenbr=14

REFERENCES

Ajani, K., & Moez, S. (2011). Gap between knowledge and nursing practice. *Procedia–Social and Behavioral Sciences*, *15*, 3927–3931. doi:10.1016/j.sbspro.2011.04.396

Altman, S. H., Stith Butler, A., & Shern, L. (Eds.). (2015). *Assessing progress on the Institute of Medicine report* The Future of Nursing. Retrieved from http://www.academicprogression.org/resources/docs/Assessing-Progress-on-the-IOM-Futue-of-Nursing-Report.pdf

American Association of Colleges of Nursing. (2006). The essentials of doctoral education for advanced nursing practice. Retrieved from https://www.aacnnursing.org/Portals/42/Publications/DNPEssentials.pdf

American Association of Critical-Care Nurses. (2017). CCRN for neonatal and CNS. Retrieved from https://www.aacn.org/certification/get-certified

American Association of Nurse Practitioners. (2013). *Nurse practitioner curriculum* [Position statement]. Austin, TX: Author. Retrieved from https://www.aanp.org/advocacy/advocacy-resource/position-statements/nurse-practitioner-curriculum

American Nurses Assocation. (2001). *Working paper on continuing professional nursing competence*. Washington DC: Author.

American Nurses Association. (2008). *Professional role competence*. Washington, DC: Author.

American Nurses Association. (2013). *Competency model*. Washington, DC: Author. Retrieved from http://www.dphu.org/uploads/attachements/books/books_5520_0.pdf

American Nurses Association. (2014). *Professional role competence* [Position statement]. Washington, DC: Author. Retrieved from https://www.nursingworld.org/practice-policy/nursing-excellence/official-position-statements/id/professional-role-competence

American Nurses Association, (2015). *Code of ethics for nurses with interpretive statements*. Retrieved from https://www.nursingworld.org/coe-view-only

American Nurses Association, (2018). *Competency model*. Retrieved from https://www.nursingworld.org/~4a0a2e/globalassets/docs/ce/177626-ana-leadership-booklet-new-final.pdf

APRN Consensus Work Group & the National Council of State Boards of Nursing APRN Advisory Committee. (2008). *Consensus model for APRN regulation: Licensure, accreditation, certification and education*. Retrieved from https://www.ncsbn.org/Consensus_Model_for_APRN_Regulation_July_2008.pdf

Bechtel, G. A., Davidhizar, R., & Bradshaw, M. J. (1999). Problem-based learning in a competency-based world. *Nurse Education Today, 19*(3), 182–187. doi:10.1016/S0260-6917(99)80003-3

Benner, P. (1982). From novice to expert. *American Journal of Nursing, 82*(3), 402–407. doi:10.1097/00000446-198282030-00004

Benner, P. (1984). *From novice to expert: Excellence and power in clinical nursing practice*. Menlo Park, CA: Addison-Wesley.

Bernikova, O. (2017). Competency-Based Education: From Theory to Practice. Proceedings of The 8th International Multi-Conference on Complexity, Informatic and Cybernetics. Retrieved from http://www.iiis.org/CDs2017/CD2017Spring/papers/ZA817SA.pdf

British Association of Perinatal Medicine. (2011). *Categories of care 2011*. London, UK: Author. Retrieved from https://www.bapm.org/sites/default/files/files/CatsofcarereportAug11.pdf

British Association of Perinatal Medicine. (2012). *Matching knowledge and skills for qualified in specialty (QIS) neonatal nurses: A core syllabus for clinical competency*. Retrieved from https://www.bapm

.org/sites/default/files/files/Matching%20Knowledge%20and%20Skills%20for%20QIS%20Neonatal%20nurses%20-%20a%20core%20syllabus%20for%20cllinical%20competency.pdf

Burke, K., Johnson, T., Sites, C., & Barnsteiner, J. (2017). CE: Original research: Creating an evidence-based progression for clinical advancement programs. *American Journal of Nursing, 117*(5), 22–35. doi:10.1097/01.NAJ.0000516248.15946.76

Chapman, H. (1999). Some important limitations of competency-based education with respect to nurse education: An Australian perspective. *Nurse Education Today, 19*(2), 129–135. doi:10.1054/nedt.1999.0620

Cline, S. (2013). *Five essential of nursing orientation*. Retrieved from http://www.healthstream.com/resources/blog/blog/2013/09/25/five-essentials-of-nursing-orientation

CompetencyWorks. (2017). What is competency-based education? Retrieved from http://www.competencyworks.org/about/competency-education

Dickerson, P., & Chappell, K. (2016). *Principles of evaluating nursing competencies*. Retrieved from https://www.td.org/Publications/Magazines/TD/TD-Archive/2016/02/Principles-of-Evaluating-Nursing-Competence

EDUCAUSE. (2014). *Competency-based education*. Retrieved from https://library.educause.edu/~/media/files/library/2014/2/eli7105-pdf.pdf

Franquis, R., & Seckman, C. (2016). Organizational readiness for nurse residency accreditation. *Journal of Professional Nurse Development, 36*(6), 309–315. doi:10.1097/nnd.0000000000000301

Great School Partnership. (2015). Hidden curriculum. In S. Abbott (Ed.), *The glossary of education reform*. Retrieved from http://edglossary.org/hidden-curriculum

Institute of Medicine. (2010). *The future of nursing: Leading change, advancing health*. Washington, DC: National Academies Press.

Institute of Medicine. (2015). *Future directions of credentialing research in nursing? Workshop Summary*. Washington, DC: National Academies Press. Retrieved from http://nap.edu/18999

International Council of Nurses. (2013). *Scope of nursing practice* [Position statement]. Retrieved from https://www.icn.ch/sites/default/files/inline-files/B07_Scope_Nsg_Practice.pdf

The Joint Commission. (2016). *Competency—Assessment of the staffing firm's staff*. Retrieved from https://www.jointcommission.org/standards_information/jcfaqdetails.aspx?StandardsFaqId=882&ProgramId=46

The Joint Commission. (2017). *Accreditation survey activity guide for health care organizations*. Retrieved from https://www.jointcommission.org/assets/1/18/2017_Organization_SAG.pdf

Kohn, L T., Corrigan, J. M., & Donaldson, M. S. (Eds.). (1999). *To err is human: Building a safer health system*. Washington, DC: National Academies Press.

Levine, J., & Johnson, J. (2012). *An organizational competency validation strategy for registered nurses*. Retrieved from http://kpnursing.org/professionaldevelopment/competencytoolkit/tools/An%20Organizational%20Competency%20Strategy.pdf

Lippincott Nursing Center. (n.d.). *Continuing education requirements for nurses by state*. Retrieved from http://www.nursingcenter.com/ceconnection/ce-state-requirements

Martin, K. (2019). MNA's Lead Nurse Planner: Supporting Contact Hours and Quality Continuing Education for Nurses. *Maryland Nurse, 20*(3), 17. Retrieved from http://search.ebscohost.com.ezproxy.umsl.edu/login.aspx?direct=true&db=cin20&AN=136478408&site=ehost-live&scope=site

Matthews, J. H. (2012). Role of professional organizations in advocating for nursing professions. *Online Journal of Issues in Nursing, 17*(1). doi:10.3912/OJIN.Vol17No01Man03

Nassari, N. (2018). *Employers benefit from offering Continuing Education for their Nurses*. Retrieved from https://www.rn.com/featured-stories/employers-benefit-from-ce-nurses/

National Association of Neonatal Nurse Practitioners. (2014). *Competencies and orientation toolkit for neonatal nurse practitioners* (2nd ed.). Chicago, IL: Author.

National Association of Neonatal Nurses. (2015). *Standard for maintaining the competence of neonatal nurse practitioners position statement #3062*. Retrieved from http://nann.org/uploads/Membership/NANNP_Pubs/Standard_for_Maintaining_the_Competence_of_NNPs-FINAL.pdf

National CNS Competency Task Force. (2010). *Clinical nurse specialist core competencies: Executive summary 2006-2008*. Retrieved from https://nacns.org/wp-content/uploads/2016/11/CNSCoreCompetenciesBroch.pdf

The National Certification Corporation. (2019). *Certification exams*. Retrieved from https://www.nccwebsite.org/certification-exams/about-certification

National Council of State Boards of Nursing. (2012). *NCSBN model act*. Chicago, IL: Author.

National League for Nursing. (n.d.). *Nurse educator core competencies*. Retrieved from http://www.nln.org/professional-development-programs/competencies-for-nursing-education/nurse-educator-core-competency

National League for Nursing. (2016). *Accreditation standards for nursing education*. Retrieved from http://www.nln.org/docs/default-source/accreditation-services/cnea-standards-final-february-201613f2bf5c78366c709642ff00005f0421.pdf?sfvrsn=10

National Organization of Nurse Practitioner Faculty. (2016). *Adult-gerontology acute care and primary care NP competencies*. Retrieved from http://c.ymcdn.com/sites/www.nonpf.org/resource/resmgr/competencies/NP_Adult_Geri_competencies_4.pdf

National Organization of Nurse Practitioner Faculty. (2017). *Nurse practitioner core competencies content*. Retrieved from http://c.ymcdn.com/sites/www.nonpf.org/resource/resmgr/competencies/2017_NPCoreComps_with_Curric.pdf

Perry, S. J., Richter, J. P., & Beauvais, B. (2018). The effects of nursing satisfaction and turnover cognitions on patient attitudes and outcomes: A three-level multisource study. *Health Services Research, 53*(6), 4943–4969. Retrieved from https://onlinelibrary.wiley.com/doi/full/10.1111/1475-6773.12997

Pew Health Profession Commission. (1995). *Critical challenges: Revitalizing the health professions for the twenty-first century.* San Francisco: Center of Health Profession, University of California.

Premji, S. S., & Hatfield, J. (2016). Call for action nurses/nursing. *Biomed Research International, 2016*, 1–5. doi:10.1155/2016/3127543

Schub, E., & Heering, H. (2016). *Clinical competencies: Assessing*. Retrieved from https://www.ebscohost.com/assets-sample-content/NRCPlus_AssessingClinicalCompetencies_NPS_SC.pdf

Swilhart, D. (2010). *How will a unit-specific competency-based orientation program benefit the new nursing staff coming to my unit?* Retrieved from http://www.strategiesfornursemanagers.com/expert_content/246879.cfm#

U.S. Department of Education. (2017). *Competency-based learning or personalized learning*. Retrieved from https://www.ed.gov/oii-news/competency-based-learning-or-personalized-learning

World Health Organization. (n.d.-a). *Neonatal mortality: Situations and trends*. Retrieved from http://www.who.int/gho/child_health/mortality/neonatal_text/en

World Health Organization. (n.d.-b). *SDG 3: Ensure healthy lives and promote wellbeing for all at all ages*. Retrieved from http://www.who.int/sdg/targets/en

Wyckoff, M. H., Aziz, K., Escobedo, M. B., Kapadia, V. S., Kattwinkel, J., Perlman, J. M., . . . Zaichkin, J. G. (2015). Part 13: Neonatal resuscitation: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation, 132*(18 Suppl. 2), S543–S560. doi:10.1161/CIR.0000000000000267

Unit VIII: Neonatal Diagnostic and Care Protocols

I

Diagnostic Processes

Samual Mooneyham

INTRODUCTION

Care of the neonate typically involves numerous diagnostic procedures and tests to identify dysfunction related to birth, prematurity, illness, or congenital malformations. This chapter highlights the commonly used methods for developing a medical or surgical diagnosis in the newborn and infant. The nursing implications for appropriate assessment of preprocedural and postprocedural care are also discussed.

Diagnostic imaging has assumed an increasingly important role in neonatal diagnosis and the assessment, evaluation, and follow-up of neonatal care. Technological advances since the 1970s have resulted in a variety of imaging modalities that demonstrate not only the internal structure but also the function of organ systems in the fetus and neonate. The spectrum of diagnostic imaging methods includes radionuclide imaging, ultrasonography, and MRI, as well as conventional roentgenologic techniques. With such an array of imaging modalities available, complex, problem-oriented decision making is required to determine which techniques should be used and which ones omitted in a particular clinical situation. In addition, diagnostic imaging examinations are expensive, with ultrasonography being the least expensive and MRI the most expensive. As the public, the government, private insurers, and the healthcare system have become increasingly cost conscious, healthcare providers have faced growing pressure to make efficacious and cost-effective decisions about the use of imaging examinations.

The selection of a particular imaging examination should be based on the risk versus benefit analysis, including consideration whether or not a particular test will result in a diagnosis. To minimize risk, consideration must be given to the size, age, and condition of the neonate.

The roles of the nurse, neonatologist, nurse practitioner, and radiologist are critically interrelated in diagnostic imaging. It is essential that the history, clinical presentation, physical examination, and laboratory data be understood so that the imaging modalities selected are the ones properly indicated for the diagnostic evaluation and subsequent therapy of the individual newborn.

Nurses should be aware of the rationale for the selection and sequencing of these diagnostic evaluations, the indications for various imaging modalities, the need for patient preparation, and the biophysical principles involved in producing the image. The nurse ensures that the correct newborn undergoes the procedure, monitors the newborn during and after the procedure, and minimizes changes in the thermal environment. The nurse may also be responsible for preparing information about the infant that is essential to the interpretation of imaging examinations. Pertinent maternal history, intrapartal complications, and gestational age must be considered. The relationship the nurse establishes with the family often provides an opportunity to inform the parents of the benefits and risks of the procedure and allows the parents to express their questions and concerns. Armed with a thorough understanding of these concepts, the nurse is able to coordinate the acquisition of diagnostic information with minimal disruption to patient care. A knowledge of patient preparation, proper positioning, and the potential risks of each procedure forms the basis of the care plans and parent teaching. These plans of care and acknowledgment of risks facilitate the development of unit policies and procedures.

DIAGNOSTIC IMAGING IN INFANTS

Diagnostic imaging in newborns and infants is unique, differing in several ways from the procedures used for older children and adults. Infants and newborns are not just small adults for whom smaller films and less exposure are all that is required. The exposure, radiation protection, and the types of diseases are different.

Conditions Requiring Diagnostic Imaging

Pathologic conditions commonly encountered in adults are often not found in infants, and many abnormal conditions are exclusive to the newborn period. Examples of these pathologic conditions are the congenital abnormalities of the newborn, genetic conditions, intrauterine growth restriction, tumors, and infections such as cytomegalovirus, toxoplasmosis, and syphilis, which can potentially be detected by diagnostic imaging (Martin, Fanaroff, & Walsh, 2015).

Anatomic Proportions

The anatomic proportions of infants are very different from those of adults, and the younger the infant, the more marked the differences. A thorough knowledge of these proportions is essential for correct patient positioning to limit field exposure and for accurate interpretation of diagnostic imaging (Dowd & Tilson, 1999; Hilton & Edwards, 2006). It is important that not only the specific area in question, but the whole of the area in question, appear in the imaging field.

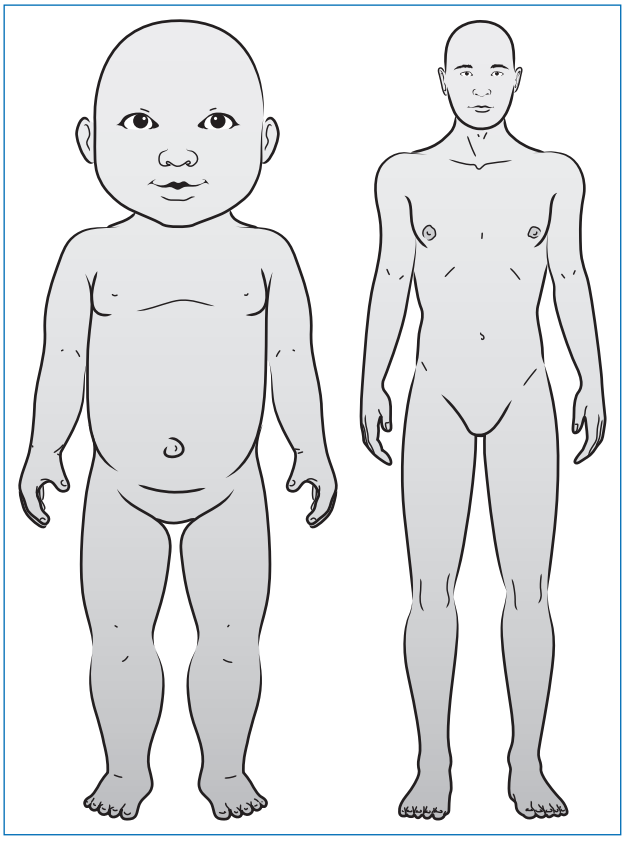

FIGURE I.1 Proportional anatomic differences between a neonate and an adult.

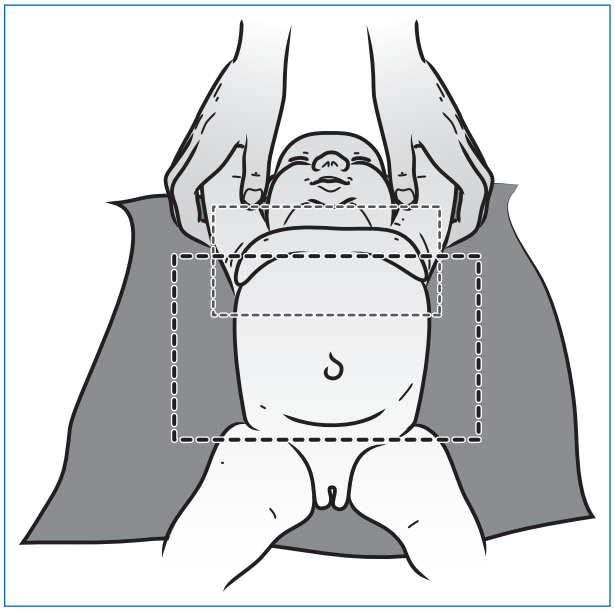

FIGURE I.2 **Neonatal radiographs should be limited to only the area of interest.** Total body radiographs should be avoided. The top box (*light dashed lines*) defines the area of interest for an anteroposterior chest radiograph. The bottom box (*heavy dashed lines*) defines the area of interest for an anteroposterior abdominal film. The gonad shield has been omitted for illustrative purposes.

As shown in Figure I.1, the newborn's head is large in proportion to the body, and the cranial vault is large in proportion to the area of the face. The neck is short, and the diaphragm is high. The kidneys are low, about midway between the diaphragm and symphysis pubis. The abdomen is large because of the relative size of the liver and stomach. The pelvic cavity is very small, and the bladder extends above the symphysis pubis. The chest, pelvis, and limbs are small in proportion to the abdomen (Hilton & Edwards, 2006; Swischuk, 1995, 2003).

In an anteroposterior (AP) projection, the neonate's lungs appear wider than they are long and much higher up in the thoracic cavity than is normally expected (Hilton & Edwards, 2006; Swischuk, 1995, 2003). The diaphragm is located just below the level of the nipples. On a lateral projection, the posterior aspect of the lungs may extend to twice the depth of the anterior part (Swischuk, 1995, 2003).

The newborn's abdomen bulges laterally wider than the pelvis, and the bulge contains abdominal organs displaced by the large liver and stomach. Care must be taken to include this area of the abdomen in the imaging field (Hilton & Edwards, 2006; Swischuk, 1995, 1997). Irradiation should encompass the smallest possible body area consistent with production of the necessary information (Dowd & Tilson, 1999). Often the field is too large, particularly in premature infants and newborns. Arms and legs should not appear on the abdominal film, nor should half the skull and abdomen appear on a chest film (Figure I.2; Hilton & Edwards, 2006; Martin et al., 2015; Swischuk, 1995, 2003).

TYPES OF DIAGNOSTIC IMAGING

Diagnostic imaging methods differ from biochemical and histologic methods in that they detect images a few millimeters in size, while biochemical and histologic methods detect changes at a molecular or cellular level.

The four major diagnostic imaging methods are x-ray (roentgenologic) imaging, radionuclide imaging, ultrasonographic imaging, and MRI (Bushong, 1999, 2000, 2003, 2013; Juhl, Crummy, & Kuhlman, 1998; Treves, 1995). This chapter discusses each of these imaging modalities in relation to the biophysical principles responsible for producing the image, the potential risks of the procedure, and the nursing care of the newborn or infant undergoing such an examination. Table I.1 summarizes the types of diagnostic imaging commonly used for neonates.

X-Ray Imaging (Roentgenology)

The principles of conventional radiography have not changed since the discovery of x-rays in the late 1800s. However, the equipment and techniques have become far more sophisticated; current radiographic methods include tomography, fluoroscopy, CT, and digital radiography.

Roentgenologic Biophysical Principles

X-rays are a form of electromagnetic energy that travel at the speed of light (about 300,000 km [186,000 miles]/second). Other forms of electromagnetic energy include gamma rays, radio waves, microwaves, and visible light. Only x-rays and gamma rays have enough energy to produce an ion pair by separating an orbital electron from its parent atom (Alpen, 1998; Bushong, 1999, 2000, 2003, 2013; Juhl et al., 1998). The amount of radiation present is measured by the detection of such ionization. Radiation exposure is measured either in units of coulombs per kilogram (C/kg) or in roentgens (1 R/258 C/kg). Although the roentgen is no longer an official scientific unit, it is still widely used in radiology. The rad is the unit of measure for the amount of radiation absorbed by the body (Alpen, 1998; Bushong, 2013; Dowd & Tilson, 1999; Juhl et al., 1998).

TABLE I.1

DIAGNOSTIC IMAGING METHODS COMMONLY USED FOR NEONATES

Technique	Indications and Advantages	Limitations	Potential Risks	Comments	Cost
Roentgenologic Techniques					
Radiographic imaging	Most frequently used initial diagnostic screening mode	Detects only four different levels of photon absorption (air, fat, water, and mineral); two-dimensional projection of 3D structures	Ionizing radiation; thermal stress of cool film plate	Proper positioning of infant is essential; child must be monitored during procedure	$
Xeroradiographic imaging	Used to evaluate soft tissue structures	Tissue structures defined by relative amounts of air, fat, water, and minerals; seldom used since advent of newer diagnostic imaging methods	Higher level of ionizing radiation than with routine radiographs	Proper positioning of infant is essential; child must be monitored during procedure	$$
Fluoroscopic imaging	Used to evaluate motion or function of cardiovascular, gastrointestinal, and genitourinary systems; may be used to guide therapeutic or diagnostic procedures	Images rely on greater radiation and/or movement of contrast material; improper diagnostic sequencing may delay informational yield; contrast material may have physiologic consequences	Much higher level of ionizing radiation than with routine radiographs; thermal stress of cool radiology environment	Proper positioning of infant is essential; child must be monitored during procedure	$$–$$$$
CT	Used to provide detailed, superior characterization of various soft tissue densities that cannot be detected by conventional radiographs	Motion artifact may cause blurring of scans; radiation dose depends on scan time; contrast material may have physiologic consequences	Ionizing radiation; thermal stress of cool environment	Proper positioning of infant is essential; child must be monitored during procedure	$$$
Ultrasound imaging	Does not use ionizing radiation, but rather uses sound waves to depict anatomic and functional motion of tissue; sound waves can be directed in a beam in a variety of planes; portable; different graphic displays are available	Ultrasound technique is operator dependent; does not provide as much information on organ functions such as urography; reveals less anatomic detail than CT; scan is adversely affected by the presence of bone and air	Thermal stress may occur with application of cool scanning gel to infant's skin; there are no known deleterious effects from clinical use of ultrasound imaging	Proper positioning of infant is essential; child must be monitored during procedure	$

(*continued*)

TABLE I.1

DIAGNOSTIC IMAGING METHODS COMMONLY USED FOR NEONATES (*continued*)

Technique	Indications and Advantages	Limitations	Potential Risks	Comments	Cost
Radionucleotide imaging	Used to trace anatomic proportions and a wide range of physiologic functions in virtually every organ in the body; amount of ionizing radiation emitted by injected agent is significantly less than the amount required for corresponding radiograph	Diagnostic yield depends on uptake of radionucleotide by different organs; radionucleotides are rarely organ specific; limited anatomic resolution	Thermal stress during nucleotide scanning	Proper positioning of the infant is essential; maximum radiation exposure is not always the organ of interest; child must be monitored during procedure	$$
PET and SPECT	Both techniques have greater sensitivity and qualifications of the distribution and density of radioactivity to depict the "metabolic" function of tissue; 3D imaging is possible with computer reconstruction; dose of nucleotide is the same; artifactual lesions can be eliminated; amount of ionizing radiation emitted by injected agents (carbon 11, oxygen 15, nitrogen 13) is significantly less than the amount required for corresponding radiograph	PET scanning requires access to a cyclotron to produce the positrons used in scans	Thermal stress during nucleotide scanning	Proper positioning of infant is essential; child must be monitored during procedure	$$$$$$
MRI	Uses magnetic fields and radio waves to produce images; the region of the body scanned can be controlled electronically, and hardware does not limit scanning sites; scans are free of high-intensity artifacts; newer scanning techniques can quantify many pathologic conditions	Availability and cost; limited use in unstable infants on life support; monitoring equipment must be free from interference with magnetic field	Does not use ionizing radiation to produce images; limited access to infant during procedure	Proper positioning is essential; must be monitored during procedure	$$$$$$

3D, three-dimensional.

When an x-ray beam is directed toward a part of the body, differential absorption of the x-ray photons by different types of body tissue occurs. A beam of x-ray photons is variously attenuated as it passes through the body tissues, producing a shadow image that is recorded on photographic film; the absorbed x-ray photons interact with the tissue, causing ionization in the body (Alpen, 1998; Bushong, 2013; Dowd & Tilson, 1999; Juhl et al., 1998). Bone and metal fragments absorb x-ray photons and therefore appear white on the radiographic film, whereas air-containing structures, such as lungs and gas-filled bowel, absorb few x-ray photons and appear black. Soft tissues and blood vessels appear as intermediate shades of gray.

A radiograph gives a two-dimensional projection of three-dimensional structures. An x-ray tube is positioned to direct the x-ray beam through the part of the neonate to be examined so as to record different views or projections on the film. This simple imaging technique can distinguish only among air, fat, and tissues with densities approximately equal to those of water or metals, but it continues to be enormously valuable and is still the diagnostic imaging method most often used in neonatal care.

X-ray photons are generated in the tungsten anode of the tube when it is bombarded by a stream of high-energy electrons emitted from the cathode (Figure I.3; Alpen, 1998; Bushong, 2013; Dowd & Tilson, 1999; Juhl et al., 1998). The energy, or penetrating power, of the resulting x-ray photons is a function of the electron energy, which is controlled by the voltage gradient across the cathode–anode gap. In diagnostic radiology, this gradient usually is 60 to 120 kV (Bushong, 2013; Dowd & Tilson, 1999; Hilton & Edwards, 2006; Juhl et al., 1998). Low kilovoltage x-rays have poor penetrating ability, whereas higher kilovoltage x-rays have deeper penetrating ability. The kilovoltage across the cathode–anode gap, therefore, controls the penetration of the x-ray beam.

The milliamperage (mA) indicates the amount of current applied to the cathode filament (Alpen, 1998; Bushong, 2013). The greater the current, the more electrons are produced for transmission across the cathode–anode gap, and the greater the number of x-ray photons generated by the anode in a finite time. The product of the exposure time and the milliamperage given to the cathode filament controls the amount, or dose, of x-rays and is expressed in milliampere-seconds (mAs; Alpen, 1998; Bushong, 2013; Dowd & Tilson, 1999; Juhl et al., 1998).

Early radiographs required an exposure time of as long as 30 minutes to produce a satisfactory image (Bushong, 2013; Juhl et al., 1998). It is not surprising, then, to find reports of radiation injury in the early days of radiology. Reports of superficial skin and tissue damage, hair loss, and anemia were common among patients and their physicians because of the prolonged exposure times and the low-energy radiation that was available. The development of an interrupterless transformer by H. C. Snook in 1907 and progressive improvements in the cathode ray tube resulted in a marked decline in reports of radiation injury. Since that time, improvements in film sensitivity and fluorescent screens have further reduced exposure times, to the point where the average exposure time for a chest radiograph is approximately one twentieth of a second (Alpen, 1998; Bushong, 2013; Dowd & Tilson, 1999; Juhl et al., 1998). The short exposure time diminishes image blurring caused by involuntary and cardiovascular motion and reduces the neonate's exposure to radiation. However, it also is important to limit the cross-sectional area of the x-ray beam to the region of interest to reduce unnecessary irradiation of adjacent organs (Alpen, 1998; Bushong, 2013; Dowd & Tilson, 1999; Juhl et al., 1998).

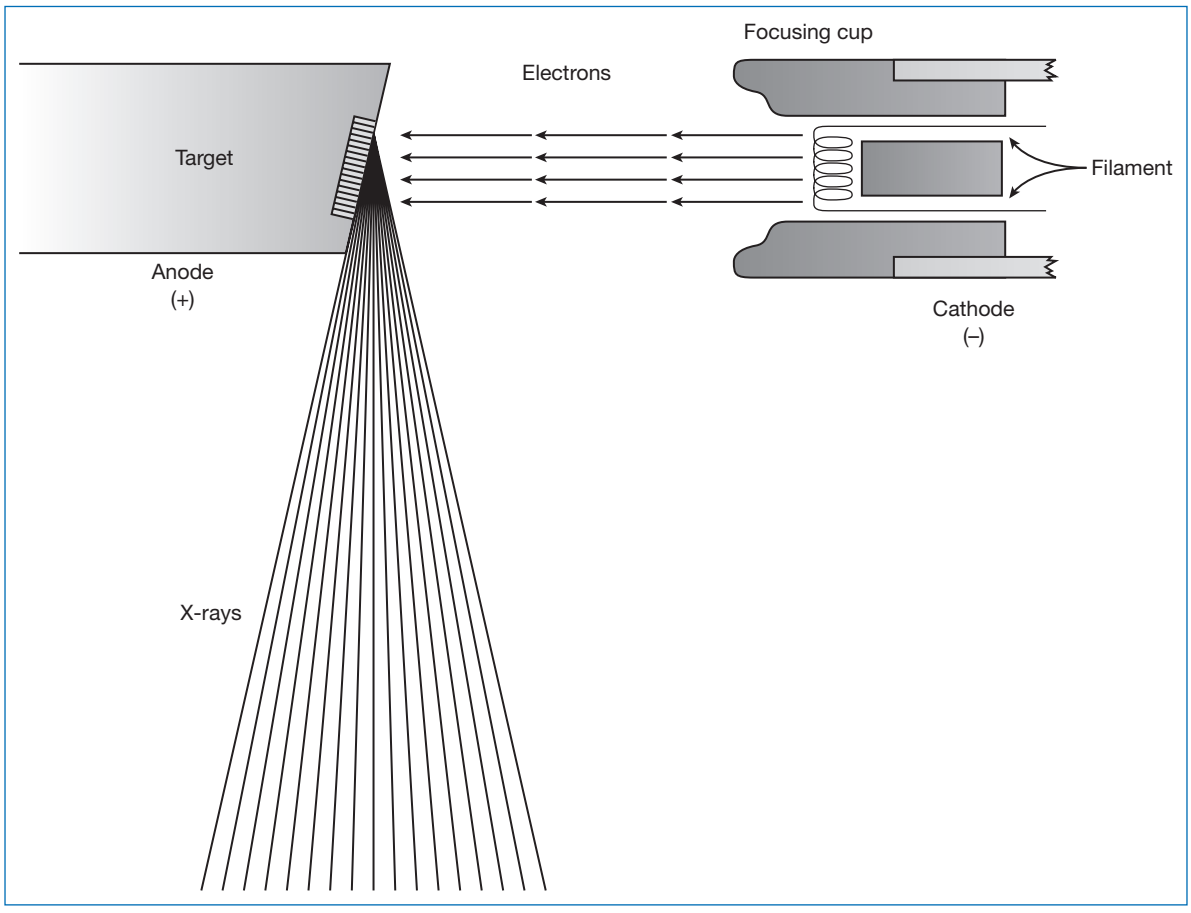

FIGURE I.3 Generation of x-ray photons in a tungsten anode–cathode tube.

Conventional radiographic images have commonly been recorded with large-size photographic film enclosed in an aluminum or plastic lightproof cassette. The film is compressed between fluorescent screens that emit visible light when exposed to x-rays. The fluorescence from the phosphor screens, rather than the direct effect of x-rays on the photographic emulsion, produces most of the image on the film (Alpen, 1998; Bushong, 2013; Juhl et al., 1998). Other diagnostic imaging methods also use ionizing radiation.

Xeroradiography. Xeroradiography is a radiographic imaging technique used to evaluate soft tissue. With this technique, the electrical charge of a photoconductive plate is altered in proportion to the intensity of the transmitted radiation image (Alpen, 1998; Bushong, 2013; Dowd & Tilson, 1999; Juhl et al., 1998). The image is recorded on the plate rather than on x-ray film. With soft tissue structures that differ only slightly in density, this method provides much better contrast than conventional radiography. It also provides an "edge effect" at the margins of discontinuous structures and therefore is indicated for the detection of nonmetallic foreign bodies and for evaluation of complex upper-airway abnormalities in the neonate (Hilton & Edwards, 2006; Juhl et al., 1998; Swischuk, 2003). Despite these benefits, the risks associated with this imaging technique must be considered. The radiation exposure involved is six to 12 times greater than that with conventional radiographs (Alpen, 1998; Hilton & Edwards, 2006; Juhl et al., 1998; Swischuk, 1995, 2003).

Fluoroscopic Imaging. Thomas Edison developed the fluoroscope in 1898 (Bushong, 2013). He focused on the use of fluorescent materials in this new imaging modality. During the period of his investigation, Edison analyzed the fluorescent properties of more than 1,800 materials, including zinc cadmium sulfide and calcium tungstate, both of which are still used. Edison halted his research in this area when his assistant and long-time friend, Clarence Dally, suffered severe x-ray burns that required bilateral upper-extremity amputation. Dally's subsequent death in 1904 is considered the first x-ray fatality (Bushong, 2013; Dowd & Tilson, 1999; Juhl et al., 1998).

Fluoroscopic imaging is a radiologic technique used to evaluate the motion of an organ system. After passing through the patient, the fluoroscopic x-rays interact with the input phosphor of the image intensifier tube. The input phosphor converts the incident x-rays into visible light, which causes the photocathode to emit electrons (Alpen, 1998; Bushong, 2013; Dowd & Tilson, 1999; Juhl et al., 1998). These electrons are accelerated and focused by electrodes in the image intensifier onto the output phosphor to produce visible light that can be viewed directly through an optical system or by a television system (Alpen, 1998; Bushong, 2013; Dowd & Tilson, 1999). Fluoroscopic images can be recorded on film or videotape. Videotape recording of fluoroscopy has become essential. It is easier and safer to rerun a videotape several times to evaluate dysfunction than to prolong the radiation exposure from fluoroscopy.

During a fluoroscopic examination, the anatomic structure may be evaluated by obtaining a spot film, which is produced by photographing the output phosphor on 100- or 105-mm film. This type of intensifier optical-coupled spot film camera reduces the radiation dose to the infant by at least 75% compared with a conventional spot film device (Bushong, 2013; Dowd & Tilson, 1999; Juhl et al., 1998; National Council on Radiation Protection and Measurements [NCRP], 1993a, 1993b, 1993c, 2018). Videotapes are used to record motions, and spot films are used to document anatomy. Although fluoroscopy has many advantages, the radiation dose delivered in 1 minute of fluoroscopy is equivalent to that of more than thirty 105-mm spot films or more than eight conventional radiographs (Alpen, 1998; Dowd & Tilson, 1999; NCRP, 1993a, 1993b, 1993c).

Electronic intensification of the faint fluoroscopic image allows fluoroscopy to be performed in subdued lighting. Improved intensifier systems have made invasive catheter studies, such as cardiac angiography, much easier to perform (Bushong, 2013; Dowd & Tilson, 1999).

Fluoroscopically guided cytologic biopsy of the lung, bone, pancreas, and lymph nodes has become possible with percutaneous needle insertion. With the aid of fluoroscopy, arteriovenous malformations can be embolized; arterial stenoses can be dilated with balloon catheters; and plastic stents can be inserted to provide drainage through biliary strictures (Hilton & Edwards, 2006; Swischuk, 1995, 2003). These surgical–radiologic procedures are needed for only a relatively small proportion of neonates; however, all fluoroscopic procedures depend on high-quality image intensification, and all require cooperation among the neonatal, surgical, and radiologic teams to achieve the best results.

Conventional X-Ray Tomography. Tomography is a radiologic method of imaging a "slice" of tissue at a specific level. Coordinated movement of the x-ray tube and the film cassette gives a defined image in the two-dimensional plane of interest, whereas the structures in front of or behind this plane are blurred out (Alpen, 1998; Bushong, 2000; Juhl et al., 1998). Tomography is useful in many circumstances, but its usefulness has been overshadowed by the development of CT.

Computed Tomography. CT was first developed in 1961 by William H. Oldendorf, and by 1973 it had become a recognized diagnostic imaging tool (Bushong, 2000). CT scanning obtains cross-sectional images rather than the shadow images of conventional radiography. Conventional radiography is based on variable attenuation of the x-ray beam as it passes through tissue. Because only the sum total of this attenuation is available for recording on the film, conventional radiography can detect only differences of 10% attenuation (Bushong, 2000, 2013; Juhl et al., 1998). Conventional radiographs, therefore, cannot produce a detailed characterization of various soft tissue densities. The densities that can be visualized on conventional radiographs are air, fat, soft tissue, and bone. CT passes multiple, highly collimated beams through the same cross-sectional slice of tissue at different angles during different intervals of time. In CT scanning, a fan x-ray beam from a source rotating about the infant passes through the body, and the exit transmission of x-ray beam intensity is monitored by a series of detectors (Alpen, 1998; Bushong, 2000). The x-ray beam "cuts a slice" from 3 to 13 mm thick through the infant. The exit transmission at any angle can be used to calculate the average attenuation coefficient along the length of the x-ray beam. By measuring the exit transmission at a large number of angles around the infant, a complex series of mathematic equations can be solved by a computer to calculate and determine the mass attenuation coefficient of small (~0.5 × 0.5 × 10 mm) volume elements, or voxels. The final cross-sectional image is made up of a display of the gray scale value of every voxel, which can be projected on a cathode ray tube and recorded photographically (Alpen, 1998; Bushong, 2000, 2013; Juhl et al., 1998). Bone is the densest, absorbs the largest amount of x-rays, and appears white; air is the least dense and appears black; soft tissues are displayed as intermediate shades of gray. CT scanning has the ability to separate spatial and contrast resolution and is much more sensitive to tissue densities than conventional radiographs. CT can distinguish differences in attenuation coefficients as small as 0.1%; it also detects changes in density in very small areas of tissue and allows identification of various components of soft tissue, such

as subarachnoid space, white matter, gray matter, and ventricles (Alpen, 1998; Bushong, 2000, 2013; Juhl et al., 1998). CT of the body is technically more difficult than cranial examination because of cardiac and respiratory motion; however, a modern body scanner can complete a scan in 2 to 4 seconds, which reduces movement artifact. In the neonate, the rapid heart and respiratory rates limit the usefulness of this technique for thoracic examination.

With CT, the density, or contrast resolution, depends on the radiation dose and scan time (Alpen, 1998; Bushong, 2000, 2013; Juhl et al., 1998). As the radiation dose (i.e., scan time) increases, the number of photons collected in each area increases and the statistical noise decreases, resulting in better contrast resolution. CT demonstrates tissue structure with precise clarity, showing superior anatomic detail compared with conventional radiographic imaging (Alpen, 1998; Bushong, 2013; Juhl et al., 1998). CT permits two-dimensional visualization of entire anatomic sections of tissue, which aids in determining the extent of the disease or malformation. Anatomic and physiologic information can be visualized despite overlying gas and bone. Contrast enhancement can measure blood flow and help define pathologic abnormalities (Bushong, 2000; Swischuk, 1995, 2003). Bolus injection of contrast material allows excellent visualization of vascular structures.

As good as CT is as an imaging modality, it is still not a radiologic microscope; CT does have its drawbacks. It also uses ionizing radiation, and because the computers require a cool room for proper equipment performance, the neonate's environment is altered significantly, a circumstance that must be considered.

Digital Radiography and Digital Vascular Imaging. Digital radiography is the term used to describe techniques that use computers to produce projectional images similar to those of conventional radiography (Bushong, 2013). Although standard CT instruments have been designed to produce two-dimensional images of two-dimensional body slices, they can also be used to project three-dimensional structures into two-dimensional images that are similar to conventional radiographs. These projections do not have the fine detail of conventional radiographs, but because the pictorial data is stored in the computer, the image can be manipulated and subtle features can be enhanced (Bushong, 2013).

Another method of digital radiography converts the image intensifier picture to digital signals that can be stored and manipulated. The most important use of this method is to obtain digital subtraction images of the heart and major arteries from data recorded before and after the injection of angiographic contrast material (Bushong, 2013). This method is much less invasive than catheterization, although the technique is new and the equipment is expensive. It has been used on a very limited basis in the neonate.

Radiographic Contrast Agents

Plain radiography can differentiate only four kinds of body tissue: tissue containing gas (lung and bowel), fatty tissue, tissue containing calcium (bone or pathologic calcifications), and tissues of water density (solid organs, muscle, and blood). To demonstrate blood vessels that are in solid organs or surrounded by muscle or to demonstrate other hollow structures, artificial radiographic contrast agents must be introduced. The contrast medium may be negative or positive and may be injected, swallowed, or administered as an enema (Hilton & Edwards, 2006; Swischuk, 1995, 2003).

Negative contrast media absorb less radiation than adjacent soft tissues and therefore cast a darker radiographic image. Gases such as air, oxygen, and carbon dioxide can be used as negative contrast media. Because negative media provide a limited amount of contrast for conventional radiography, they are seldom used (Martin et al., 2015; Swischuk, 1995, 2003).

Box I.1

RADIOPHARMACEUTICALS USED IN NEONATAL DIAGNOSTIC IMAGING

- Technetium 99m
  - *Sulfur or tin colloid:* used for imaging liver, spleen, bone marrow, ventilation, and gastrointestinal bleeding
  - *Albumin microspheres:* used for imaging lung perfusion
  - *Pyrophosphate, diphosphate:* used for imaging skeletal and myocardial infarcts
  - *Pertechnetate:* used for imaging thyroid, brain, and gastrointestinal tract
  - *Diethylenetriaminepentaacetic acid (DTPA) glucoheptonate:* used for imaging kidney and brain
  - *Hepatoiminodiacetic acid (HIDA):* used for imaging biliary system
- Iodine 131: used for imaging thyroid and fibrinogen and for clot localization
- Xenon 131, krypton 81m: used for imaging lung ventilation
- Thallium 201: used for imaging myocardial perfusion and for testicular localization

Positive contrast media use elements with a high atomic number, which absorb much more radiation than surrounding soft tissues and therefore cast a lighter image. Barium and iodine are the two elements currently used. Barium sulfate, a relatively stable, nontoxic compound, is the major contrast agent used for outlining the walls of the GI tract. Iodine-containing salts that are excreted by the kidneys are used for a wide variety of urographic and angiographic studies. The kidneys also excrete the newer nonionic, iodine-containing media. Because of their lower osmolality, these agents are less painful than iodine-containing salts when injected into arteries, and they are rapidly replacing the older contrast agents (Box I.1; Hilton & Edwards, 2006; Martin et al., 2015; Swischuk, 1995, 2003).

Ionizing Radiation Interactions With Tissue

When an infant undergoes a radiologic procedure, most of the radiation passes through the infant's body and strikes the fluorescent screens encompassing the film. The roentgen (or C/kg) is a measure of how many x-rays were present. For the infant, the more important quantity is the number of x-rays that stop in the body and how much energy they deposit. The radiation dose (rad) is a measure of the energy deposited. X-rays that pass through the infant are attenuated by photoelectric absorption and Compton scattering (Alpen, 1998; Bushong, 2013; Dowd & Tilson, 1999; Juhl et al., 1998).

Photoelectric absorption involves the complete interaction and absorption of the incoming x-ray photon by the atom. The photoelectric interaction declines rapidly with increasing energy and increases rapidly with increasing atomic number (Alpen, 1998; Bushong, 2013). This is why lead is such an effective shield and bone is so much more absorptive than soft tissue.

Compton scattering is the phenomenon in which only part of the energy of the incoming x-ray photon is transferred to the atom; this reduces the energy of the original photon and produces a scattered electron (Bushong, 2013).

With ionizing radiation, electrons are removed from their atoms and endowed with energies 14 to 20,000 times greater than those in ordinary biochemical reactions (Alpen, 1998; Bushong, 2013; Dowd & Tilson, 1999; Juhl et al., 1998). These electrons can maraud through tissue for some distance and can break any kind of chemical bond in the body (Bushong, 2013; Dowd & Tilson, 1999; NCRP, 1993a, 1993b, 1993c). In biochemical systems the reactions are carefully controlled, often by a special geometric juxtaposition of the reactants. A high-speed electron is akin to a bull in a china shop; it can break anything, anywhere. Once it has ripped an electron out of an atom in a molecule, the molecule itself is placed at such a high-energy level that it can produce all kinds of chemical reactions that would never have been possible without ionizing radiation (Alpen, 1998; Bushong, 2013; Dowd & Tilson, 1999; NCRP, 1993a, 1993b, 1993c).

X-rays and gamma rays are identical in nature except that, in general, x-rays are made in high-voltage machines, whereas gamma rays originate from the nuclei of atoms. Radiations emitted from such naturally unstable atoms as uranium are commonly more energetic per unit than x-ray photons. For example, gamma rays are commonly measured in millions of electron volts (meV) per photon, whereas x-rays are commonly measured in 50 to 100 kiloelectron volts (keV; 50,000–100,000 eV). Gamma rays from unstable nuclei do all the things that x-rays do; that is, they can undergo photoelectric and Compton effects, and they can produce high-energy electrons and positrons (Bushong, 2013; Dowd & Tilson, 1999).

Other radiation decay products also create particulate radiation called alpha and beta rays. Beta rays are not truly rays but high-speed electrons emitted from the nuclei of decay products of uranium (Alpen, 1998; Bushong, 2013; Dowd & Tilson, 1999). Alpha particles are emitted from the nuclei of uranium. Alpha particles are the "stripped" nuclei of helium and consist of any two protons. Ultimately, the two protons find two electrons in the environment and become helium gas. X-rays and gamma rays, which pass through the body and do not produce effects on tissue, have no biologic effect. However, alpha and beta particles interact at every millimeter along their path through tissue, so if they gain access to tissue, biologic harm is guaranteed (Bushong, 2013; Dowd & Tilson, 1999; NCRP, 1993a, 1993b, 1993c).

Biologic damage from ionizing radiation depends on the amount of energy deposited in a particular tissue. X-rays and gamma rays produce harmful effects only to the extent that they put high-speed electrons in motion. If the same number of electrons is put in motion by gamma rays from plutonium or from deposited radionuclide or by agents from external x-rays, the biologic effects are the same (Bushong, 2013; Dowd & Tilson, 1999; NCRP, 1993a, 1993b, 1993c).

Factors Affecting Radiographic Quality

Interpretation of a neonatal radiograph requires a rapid evaluation to determine whether the radiograph is technically satisfactory. Several factors determine the technical quality of a radiograph, including film exposure, phase of respiration, motion, tube angulation, and infant positioning. If one of these factors is unsatisfactory, the film may be misinterpreted. When nurses have an understanding of these factors, the technical quality of radiographs is improved.

Film Exposure. A reasonable criterion for judging film exposure is satisfactory visualization of the dorsal intervertebral disk spaces through the entire cardiothymic silhouette (Hilton & Edwards, 2006; Martin et al., 2015; Swischuk, 1995, 2003). If the film is underexposed, the dorsal disk spaces are lost, and the lungs and other structures have a homogeneous, "whitewashed" appearance. If the film is overexposed, the pulmonary vascular markings are progressively lost until the lungs have a black, "burned out" appearance (Hilton & Edwards, 2006; Swischuk, 1995, 2003).

Phase of Respiration. The phase of respiration at the time the film is obtained affects the appearance of the radiograph considerably (Figure I.4). On an expiratory film, the heart may appear grossly enlarged, the lung fields may appear opaque (which may simulate diffuse atelectasis), and the diaphragm is located above the seventh rib (Hilton & Edwards, 2006; Swischuk, 1995, 2003). On an inspiratory film, the diaphragm is at the eighth rib, the cardiothymic diameter is normal, and the pulmonary vascularity is prominent. The right hemidiaphragm is slightly higher than the left. If the right hemidiaphragm is at or above the level of the seventh rib, the film was obtained in the expiratory phase or the infant has hypoaerated (Hilton & Edwards, 2006; Swischuk, 1995, 2003).

Motion. If the infant moves just as the radiograph is made, the resulting film is blurred. Motion causes blurring of the hemidiaphragms, the cardiovascular silhouette, and all fine pulmonary detail (Hilton & Edwards, 2006; Swischuk, 1995, 2003). Movement blur on diagnostic images can be prevented by fast imaging and adequate immobilization.

Speed. A short exposure time is essential for obtaining clear images. This can be achieved by limiting the duration of exposure to the energy source and by increasing the use of computed imaging.

Immobilization. The nursing staff is primarily responsible for ensuring adequate immobilization during diagnostic imaging. Inadequate immobilization is an important cause of poor quality on neonatal images. Proper immobilization techniques improve

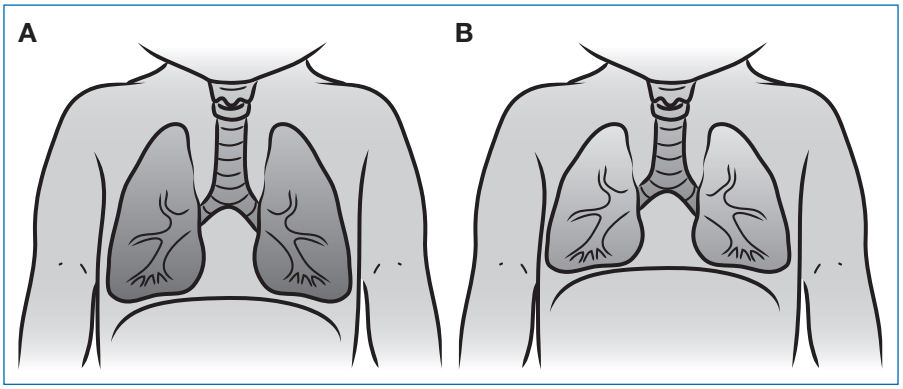

FIGURE I.4 Differences in appearance between inspiration (A) and expiration (B) in a neonatal chest radiograph. On full inspiration, the diaphragm is located at the eighth rib, and the lungs appear larger and darker. During expiration, the diaphragm is at or above the seventh rib, and the lung fields appear smaller and lighter. The heart size may also appear larger on expiratory films.

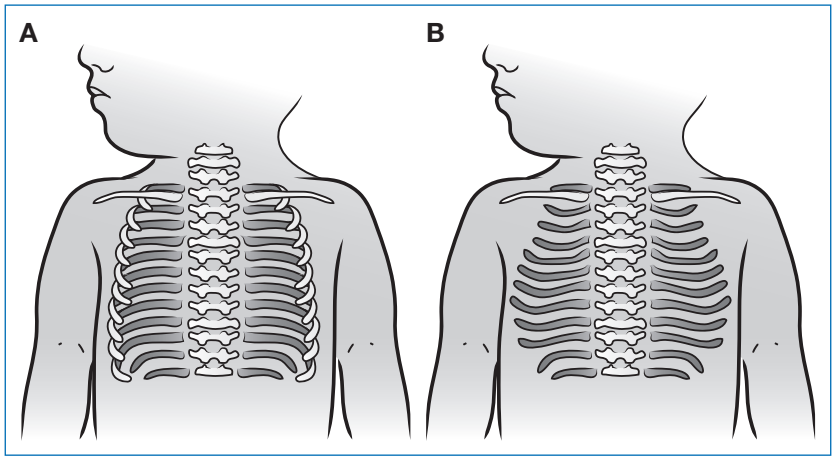

FIGURE I.5 Skeletal position in a normally positioned radiograph (A) and in a film obtained with cephalad positioning of the x-ray tube (B).

image quality, shorten the examination time, and eliminate the need for repeat studies (Hilton & Edwards, 2006; Swischuk, 1995, 2003). Proper immobilization may be less traumatic than manual restraint alone. An immobilization board may be required, or tape, foam rubber blocks and wedges, towels, diapers, or clear plastic acetate sheets may be used.

Physical risks to neonates are associated with immobilization. The type of restraint or an ill-designed immobilization device may cause trauma. Tape or plastic sheets may cause skin and soft tissue damage if not applied and removed carefully. Also, thermal stress may be a factor when a neonate is placed on a noninsulated board or film cassette. The nurse should position and immobilize the infant properly so that the technician can center the tube, position the beam, and make the exposure. If the nurse and the technician work together, superior results are achieved with greater speed and less disruption than if they worked separately.

Infants lie still only when they are very ill. Otherwise, they greatly resent being forcibly restrained, especially in an unusual position. A number of immobilization devices are available, but the best means is a pair of adequately protected adult hands (Hilton & Edwards, 2006; Swischuk, 1995, 2003).

Tube Angulation. Another factor that affects radiographic quality is angulation of the x-ray tube, along with improper field limitation. Often on neonatal films, the infant's chest appears mildly lordotic, with the medial clavicular ends projected on or above the dorsal vertebrae. This results in a rather peculiar chest configuration. The preossified anterior arcs of the upper ribs are positioned superior to the posterior arcs (Figure I.5). The lordotic projection tends to increase the apparent transverse cardiac diameter, making it difficult to determine the size of the heart. Lordotic projections result when the x-ray tube is angled cephalad, when the x-ray beam is centered over the abdomen, or when an irritable infant has arched the back at the time of the film exposure. If the x-ray tube is angled caudad, or the x-ray beam is centered over the head, the anterior rib arcs are angulated sharply downward in relation to the posterior arcs (Hilton & Edwards, 2006; Swischuk, 1995, 2003).

Infant Positioning. Proper infant positioning is important for radiographic quality and interpretation. If the infant is rotated, a false impression of a mediastinal shift may be created (Figure I.6). The direction and degree of rotation can be estimated by comparing the lengths of the posterior arcs of the ribs from the costovertebral junction to the lateral pleural line at a given level. The infant is rotated toward the side with the greatest posterior arc length (Hilton & Edwards, 2006; Swischuk, 1995, 2003).

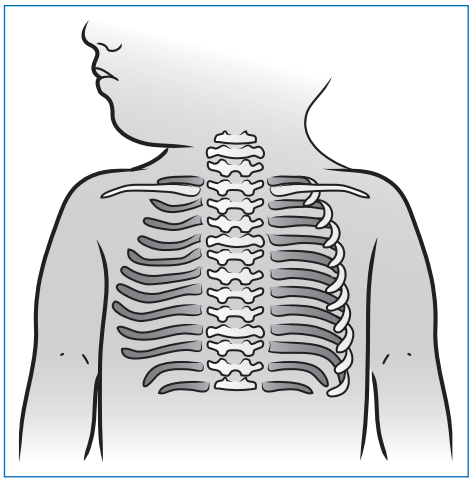

FIGURE I.6 Skeletal configuration in a film obtained with the infant rotated to the right.

Another measurement for determining the degree of rotation is the distance from the medial aspect of the clavicles to the center of the vertebral body at the same level. If the infant is properly positioned, the medial aspects of the clavicles should be equidistant from the center of the vertebral body (Hilton & Edwards, 2006; Swischuk, 1995, 2003). The distance is greater on the side toward which the infant is rotated. On a lateral view, rotation can be readily determined by observing the amount of offset between the anterior tips of the right and left sets of ribs.

Before any chest film is interpreted, these factors must be systematically evaluated. Through experience, this evaluation becomes automatic, and the film can be scanned rapidly.

Radiologic Projections

Radiologic projections are the geometric views of the radiograph, and they vary among institutions and radiologists. They can be customized to the specific infant or clinical condition. For example, the skull may require a simple AP film to make the diagnosis of a fracture, whereas a complete skull series may be necessary for evaluation of congenital malformations. In the neck and upper airway, a lateral film in inspiration with the infant's head extended may be sufficient for the evaluation of stridor, or a xeroradiography of the soft tissue structures of the neck may be required. Because the radiation dose is much greater with a xeroradiography

than with a plain lateral neck film, the indications for this examination should be clear (Swischuk, 2003).

For evaluation of the spine, the AP projection is most commonly used. Oblique views of the spine usually are difficult to obtain in infants because it is difficult to position and immobilize babies. Also, the diagnostic information gained does not outweigh the risk of the greater radiation exposure required to obtain such views. For evaluation of congenital hip dysplasia, an AP view of the entire pelvis and both hips is required. Gonadal exposure should be minimized with proper shielding during radiographic examination of the hips. Assessment of skeletal maturation in the infant requires an AP film of the left hemi skeleton, and a long bone series requires a film of the upper and lower extremities (Hilton & Edwards, 2006; Swischuk, 1995, 2003).

Chest radiographs are the most frequently performed diagnostic imaging procedure in the NICU. In most cases an AP projection from a supine position is satisfactory for evaluating the infant's chest, heart, lung fields, endotracheal tube, line placement, and pneumothorax (air leak complications related to mechanical ventilation). The cross-table view allows verification of the pleural chest tube being placed anteriorly or posteriorly. Lateral decubitus is used to evaluate small pneumothorax and small pleural fluid collection; these can be hard to see on an AP view. The upper right reveals abdominal perforation, which shows free air under the diaphragm (rarely used). Lateral projections of the chest often are poorly positioned, have diminished technical quality, and require greater radiation exposure of the infant. For the experienced radiographer, an AP film in the supine position is sufficient in most cases. In rare cases, a lateral chest film with esophageal barium contrast may be requested for evaluation of the left atrium of the heart (Gomella, Cunningham, & Eyal, 2013; Hilton & Edwards, 2006; Swischuk, 1995, 2003; Verklan & Walden, 2014).

Abdominal x-ray films are also frequently obtained in the NICU. The most commonly used radiographic projections are the AP, cross-table lateral, and left lateral decubitus views. Because the infant's abdomen is relatively cylindric, a lateral view provides more information than it does in an older child or adult. AP views define the gas pattern, intestinal displacement, some masses, ascites, and placement of lines such as umbilical catheters or intestinal tubes, whereas the cross-table lateral view is recommended in the diagnosis of abdominal perforation, and the left lateral decubitus view is for diagnosis of intestinal perforation, and free intra-abdominal air (Gomella et al., 2013; Hilton & Edwards, 2006; Swischuk, 2003).

Exposure Factors in Infancy

Numerous radiographic variables are involved in x-ray exposure. The x-ray machine, films, screens, types of cassette, and processing methods, as well as the radiologist's preference, may vary greatly from one department and institution to another. However, a few general principles can be stated:

1. Exposure time should be kept short to prevent movement blur and to limit the radiation dose.
2. Radiographic technicians should be knowledgeable about factors and variables that affect exposure so that repeat films occasioned by poor technique on the initial radiograph can be avoided.
3. A repeated infant x-ray is the major cause of the largest dose of unnecessary radiation (Hilton & Edwards, 2006; Swischuk, 1995, 2003); every possible precaution should be taken to ensure that the first attempt produces a film of diagnostic quality.
4. Before a repeat is done, the film should be shown to the radiologist or neonatologist who requested it; although the technical quality may not be ideal, the film may provide sufficient information.

Radiation exposure can also be reduced by using other diagnostic imaging modalities, when possible, that do not use ionizing radiation to create an image (e.g., ultrasonography, MRI; Swischuk, 1995, 2003). If radiologic imaging is the best diagnostic approach for the infant's condition, it may be important to "customize" the examinations, to limit the area examined, and to reduce the number of follow-up films. The radiologist and technician should be knowledgeable about the rapid technologic advances in film–screen combinations, filtration, projections, and film processing, which can help produce a film of fine diagnostic quality while minimizing radiation exposure (Alpen, 1998; Swischuk, 1995, 2003).

Ideally, there would be no "routine" radiologic examinations, just problem-oriented procedures. However, there is a logical approach to radiographic examinations. Plain films should be obtained first. Then, if indicated, a dye contrast study (e.g., excretory urography) should be performed, because the contrast material is rapidly eliminated from the body. Last, barium contrast studies should be obtained. Barium contrast studies are performed after the others because (1) barium interferes with any nuclear scintigraphic scans, body-computed tomograms, and ultrasonographic scans and (2) barium is slowly eliminated from the GI tract, which delays further diagnostic evaluation. Additional radiation exposure is possible if the barium must be completely eliminated before the next imaging procedure (Hilton & Edwards, 2006; Swischuk, 1995, 2003).

Adequate patient preparation is another means of reducing radiation exposure (Hilton & Edwards, 2006; Swischuk, 1995, 2003). If GI and genitourinary (GU) imaging are both to be performed, the GU examination should be scheduled first. Although each institution has its own policies, in preparation for a GU examination such as excretory urography, the infant should be kept on nothing by mouth (NPO) status for no longer than 3 hours; this can be accomplished by withholding the early morning feeding and scheduling the examination for 8 a.m. No preparation is necessary for excretory urography in infants with abdominal masses, trauma, or GU emergencies. If the infant has impaired renal function, the radiologist and the neonatologist should discuss the condition thoroughly so that the risks of this procedure are minimized. For an infant who has been feeding, the baby is prepared for a GI contrast study by keeping the child on NPO status for no longer than 3 hours before the examination. Generally, if a contrast study of the entire GI tract has been requested, the lower GI series is performed before the upper GI series (Hilton & Edwards, 2006; Swischuk, 1995, 2003). This allows time for elimination of the barium in the colon and prevents the barium from interfering with the diagnostic quality of the upper GI study. Colon preparation is usually unnecessary in the neonate and should be avoided in infants with an acute abdominal condition and in those suspected of having Hirschsprung disease (Swischuk, 1995, 2003).

Collaborative Care

Radiation Protection. Any radiation is considered harmful to the infant, and all efforts must be made to reduce radiation exposure without forgoing diagnostic information. Radiation exposure can have both genetic and somatic effects (Bushong, 2013; Dowd & Tilson, 1999; NCRP, 1993a, 1993b, 1993c). Reduction of radiation exposure should be the goal for sites that are sensitive genetically (gonads) and somatically (eyes, bone marrow). Although there is no evidence that somatic damage (e.g., carcinogenesis or cataracts) occurs as a result of low-dose diagnostic radiologic procedures, dose reduction should be accomplished for the site examined and for the rest of the body (Dowd & Tilson, 1999). Methods of reducing

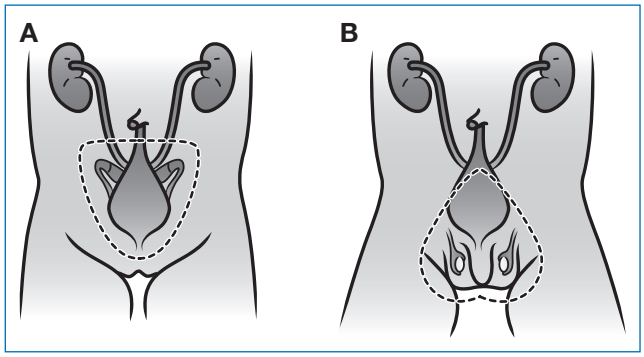

FIGURE I.7 Anatomic placement of gonad shield for female infants (A) and for male infants (B).

radiation exposure include performing examinations only when they are clinically indicated, selecting the appropriate imaging modality, using the lowest radiation dose that achieves an image of diagnostic quality, avoiding repeat examinations, reducing the number of films obtained, using appropriate projections with tight field limitation, ensuring proper positioning and immobilization, and shielding the gonads (Alpen, 1998; Dowd & Tilson, 1999; Hilton & Edwards, 2006; NCRP, 1993a, 1993b, 1993c).

If the gonads are not within the area of interest, gonadal exposure depends on the adequacy of field limitation. The maximum gonadal dose occurs when the gonads are unshielded and exposed to the primary x-ray beam. This dose declines rapidly as the distance from the gonads to the primary beam increases. Gonadal exposure in an AP film that includes the gonads can be reduced by 95% with proper contact shielding (Dowd & Tilson, 1999). The gonads should be shielded whenever they are within 5 cm of the primary x-ray beam.

Contact gonadal shields are easy to make from 0.5-mm thick lead rubber sheets, and they should be sized for gender and age (Figure I.7; Swischuk, 1995, 2003). In males, proper positioning of the shield avoids obscuration of any bony detail of the pelvis if the upper edge of the shield is placed just below the pubis and if the testicles have descended into the scrotum. In females, the position of the ovaries varies with bladder distention. Because of their anatomic location, the ovaries cannot be shielded without obscuring lower abdominal and pelvic structures. The lower margin of the gonad shield should be placed at the level of the pubis, and the upper margin should cover at least the lower margin of the sacroiliac joints (Hilton & Edwards, 2006; Swischuk, 1995, 2003).

Radiation Safety. The three ways to reduce radiation exposure of personnel are: (1) shorten the duration of radiation exposure; (2) increase the distance from the radiation source; and (3) provide radiation shielding between the nurse and the radiation source (Alpen, 1998; Bushong, 2013; Dowd & Tilson, 1999; NCRP, 1993a, 1993b, 1993c). Portable radiologic examinations are the most common form of diagnostic imaging routinely performed in the NICU. During these procedures, there is a tendency for all the nurses to leave the room when an exposure is being produced; consequently, other infants may be left unattended for that short period. Because of this practice, parents have expressed fear about their infants facing environmental radiation hazards.

Using the example of an infant who receives two radiologic examinations per shift, the total dose outside a 30-cm (1 foot) radius of the primary beam is 70 μR. If the staff nurse worked a 250-day work year and held an infant who received two x-ray examinations per shift, the cumulative dose would be 18,000 μR (18 mrad)/year (1,000 μR = 1 mrad). This value is considerably lower than the background radiation in a building, which amounts to 100 to 150 mrad/year (Bushong, 2013; Dowd & Tilson, 1999).

Other radiologic studies done in the NICU have found that within 1.82 m (6 feet) of the target, an unshielded person receives 100 mrad *per hour of exposure*. Because the duration of exposure is approximately 0.1 second, the radiation dose is 0.003 mrad/exposure. This amount of radiation is far below the safety limit of 500 mrad/year. At this rate of radiation exposure, a full-time staff nurse would have to be exposed to more than 6,000 x-rays each day to reach the radiation safety limit per year (NCRP, 1993a, 1993b, 1993c).

It appears that if certain basic radiation precautions are observed, nurses and other NICU personnel need not leave the room during x-ray exposures. However, staff members should stay 30 cm (1 foot) or farther from the infant being radiographed. Care must be taken to ensure that if a horizontal beam film is obtained (e.g., in a cross-table lateral projection), no one is in the direct x-ray beam because the radiation dose in the primary beam is considerably higher than in the scattered portion. When a horizontal beam is used, it should not be directed at any other patient or person. Any employee within 30 cm (1 foot) of the incubator or one who is holding the infant for the exposure should wear a lead apron and gloves.

The x-ray beam must be confined to the area within the cassette edges. An infant causes little scatter, but an adult's hands can easily come within the field of primary radiation and cause scatter. It is important to position and secure the infant properly while keeping the hands out of the x-ray beam. If correct radiographic technique is used, the dose to the nurse's lead-protected hands is approximately 0.01 mSv (millisieverts). The annual dose limit to the hands of nondesignated personnel is 500 mSv.

Table I.2 summarizes the process of systematic interpretation of radiographic images in the neonate.

Radionuclide Imaging

The use of radioisotopes has brought a new dimension to diagnostic imaging, because they can be used to trace a wide range of physiologic functions in virtually every organ in the body, thereby complementing conventional radiography and ultrasonographic imaging. The difference between conventional radiography and radionuclide imaging is that with the former, images are produced by the transmission of radiation, whereas with the latter, images are produced by the emission of radiation (gamma rays) previously introduced into the body and recorded on film or in a computer (Figure I.8; Alpen, 1998; Bushong, 2013; Dowd & Tilson, 1999; Juhl et al., 1998; Treves, 1995).

Radionuclide studies yield both physiologic information and anatomic representations of the distribution of radioactivity, depending on the selective uptake of radionuclide by different organs of the body (Bushong, 2013; Dowd & Tilson, 1999; Treves, 1995). The primary disadvantage of radionuclide imaging is the limited anatomic resolution to diameters greater than 2 cm.

Biophysical Principles. Relatively small amounts of radioactivity are used in radionuclide imaging, and the radiation hazard is significantly smaller than for corresponding conventional radiographic investigations (Bushong, 2013; Dowd & Tilson, 1999; Treves, 1995). The radioactive substance injected is usually distributed throughout the body, and the site of maximum radiation is not always the organ under investigation (Bushong, 2013; Dowd & Tilson, 1999; Treves, 1995). For example, the thyroid gland selectively concentrates radioactive iodine, even if this compound is being used to study another organ. In this case, thyroid iodine uptake can be blocked pharmaceutically. The kidneys excrete the

TABLE I.2

RADIOGRAPHIC INTERPRETATION

Technical Evaluation	Characteristics
Film density and contrast	The intravertebral disk spaces should be visible through the cardiothymic silhouette. Underexposed films appear whitish with progressive loss of spaces; overexposed films have a "burned out" appearance with loss of pulmonary vascular markings.
Phase of respiration	The respiratory phase affects the appearance of the lung fields. During expiration, the cardiothymic silhouette appears larger, and the lung fields appear more opaque; the hemidiaphragms are usually at the level of the seventh rib. During inspiration, the cardiothymic silhouette is normal, pulmonary vascularity is seen, and the lung fields are clear. Adequate inspiration puts the right hemidiaphragm at the level of the posterior eighth rib; the right hemidiaphragm usually is slightly higher than the left during basal breathing.
Motion	Radiology personnel must check for motion at the time the film is taken. Motion is detected by blurring of the hemidiaphragms and cardiothymic silhouette. Motion obscures all fine pulmonary vascular detail, which makes the films unsatisfactory for evaluation of the lung fields.
Tube angulation and patient positioning	AP films of the newborn appear lordotic, with the medial ends of the clavicles projecting on or above the second dorsal vertebra. If the tube has been angled cephalad, the lordosis is exaggerated, with the anterior arcs of the ribs positioned superior to the posterior arcs. The cardiothymic silhouette appears larger because the view is through the transverse diameter of the heart. This occurs if the infant arches during the procedure or if the beam has been centered over the abdomen. Caudad angulation of the beam over the head results in distortion of the chest, with the anterior ribs' arcs angled sharply downward in relation to the posterior arcs.
Rotation of the patient	Assessment of rotation is critical in determining whether mediastinal shift is present. Lateral rotation may lead to the false impression of a mediastinal shift. The trachea shifts toward the side of the rotation, and the contours of the heart are altered. The direction and degree of rotation are estimated by comparing the lengths of the posterior arcs of the ribs on both sides. The side with the longest posterior arc is the side to which the patient is rotated. Rotation also results in unequal lengths of the clavicles when they are measured from the medial aspects to the center of the vertebral body at the same level. The patient is rotated to the side with the longer clavicle.
Heart size and pulmonary vascularity	These features are difficult to determine in the newborn in the first 24 hours of life because of the dynamic cardiovascular alterations that occur during this period. Changes in the transitional circulation are associated with an increase in pulmonary blood flow and in blood return to the left atrium, a decrease in blood return and lower pressure in the right atrium, and changes in systemic and pulmonary arterial pressures. The newborn's heart size is relatively larger in the first 48–72 hours because of those rapid changes. Heart size can be accurately assessed only during basal breathing because the size is significantly altered during phases of the cardiac cycle and during hyperexpansion of the lung. After the first 24 hours, a cardiothoracic ratio above 0.6 is the upper limit of normal. Fetal lung fluid is reabsorbed, and the air spaces are filled with air on inspiration. The resorption of lung fluid enhances the appearance of the pulmonary lymphatics, resulting in an apparent increase in vascularity at birth. Transient tachypnea of the newborn is characterized by perihilar streaky infiltrates with increased pulmonary vascularity and good lung inflation.
Cardiothymic silhouette	The cardiac configuration is difficult to determine in the newborn largely because of the variation in size and shape of the thymus. The aortic knob and main pulmonary artery are obscured by the thymus, which frequently has a wavy border. A tuck may be seen in the left lobe of the thymus at the lateral margin of the right ventricle, a feature called a sail sign. The apex of the heart has a more cephalad position and assumes a more caudal position over time. The elevation of the apex is due to the relative right ventricular hypertrophy of the fetus. After birth, as the left ventricle becomes more prominent, the cardiac apex descends. The thymus involutes rapidly under the stress of delivery and over the next 2 weeks of life may enlarge slightly.
Aeration of the lungs	Satisfactory inspiration positions the hemidiaphragms at the posterior arcs of the eighth rib. Expansion and radiolucency of the right and left sides are equal. If the sides are not comparable, a right and left lateral decubitus film should be obtained to evaluate for fluid levels or air. The lungs may bulge slightly through the ribs. On lateral projection, the hemidiaphragms should be smoothly domed. The AP and transverse diameters of the chest vary with age and disease. In a normal

(*continued*)

TABLE I.2

RADIOGRAPHIC INTERPRETATION (*continued*)

Technical Evaluation	Characteristics
Aeration of the lungs (*cont.*)	newborn, the AP and transverse diameters are equal. Over time, the transverse diameter increases, giving the chest cavity an oblong appearance. Air-trapping diseases produce a more rounded configuration, whereas hypoaeration results in a more flattened AP diameter. With hypoaeration, the right hemidiaphragm is located at the seventh rib, the posterior arcs have a more downward slope, and the transverse diameter of the chest is reduced. Laterally, hypoaeration results in increased doming of the diaphragm. With hyperaeration, the hemidiaphragm is located below the level of the ninth rib, the diaphragm is flattened, and the posterior rib arcs are horizontal. Hyperaeration also results in greater bulging of the lungs through the intercostal spaces and an increased diameter of the upper thorax.
Pulmonary infiltrates	Films should be evaluated for areas of increased pulmonary lucency or density. The characteristics and distribution of densities may lead to a diagnosis. Infiltrates should be described with regard to their distribution (unilateral, bilateral) and nature (alveolar, reticulated, diffuse, nondiffuse, patchy, streaky).
Mediastinal shift	The examiner evaluates for mediastinal shift by determining if the trachea, heart, and mediastinum are in normal position. In general, the shift occurs toward the side with the diminished lung volume or away from the hemithorax with the increased lung volume. Rotation of the patient must first be excluded.
Liver size	The edges of the liver should be clearly defined, and the size of the organ should correlate well with the size determined by palpation, especially when the intestines are filled with air. If insufficient gas is present in the abdomen, the size of the liver cannot be determined. Atelectasis obscures the upper margin of the liver. Radiographically, the size of the liver is not altered by the phase of respiration, as it is during palpation. Liver size may vary with the progression of right-sided heart failure. The position of the liver may be altered by congenital malformations such as situs inversus.
Abdominal gas pattern	Swallowing air produces gas in the stomach. The gas pattern must be interpreted in light of the infant's history. In the newborn, stomach air is present, with progression of air through the small bowel at 3 hours of life and rectal air by 6 hours. With bowel obstruction, gaseous distention progresses until at some point the bowel is blocked; beyond that point there is a paucity of air or a gasless bowel. Lack of haustra in the colon makes it possible to distinguish the small and large bowels on the radiograph. A gasless abdomen may be seen with prolonged gastrointestinal decompression, severe dehydration, acidosis, oversedation, brain injury, diaphragmatic hernia, midgut volvulus, and esophageal atresia. Marked aerophagia may be due to mechanical ventilation, tracheoesophageal fistula, necrotizing enterocolitis, and mesenteric vascular occlusion. Free peritoneal air rises to the highest level and outlines superior structures; therefore, it is best demonstrated on a left lateral decubitus film.
Catheter and tube positions	All catheter and tube positions should be evaluated and reported each time a radiograph is made. The position of these devices may provide clues to the underlying disease, and malpositioning of tubes and catheters may be life threatening. The trachea is positioned to the right in the midmediastinum, anterior and slightly to the right of the esophagus. The carina is located at T4. In the right aortic arch, the trachea is found slightly to the left of the vertebral column. Endotracheal tubes optimally are placed in the midtrachea. If the tip is too low (below T4) or too high (above the thoracic inlet), ventilation is suboptimal. Inadvertent esophageal intubation has occurred when the tip of the tube is below T4 but is still in the midline or when the trachea can be visualized apart from the tube. NG tube placement should be reported. NG tubes may be too short (seen in the distal esophagus) or too long (seen in the duodenum or jejunum), or they may be coiled in the esophagus (tracheoesophageal atresia). The location of vascular catheters must be evaluated. Central catheters should be placed with the tip in the superior part of the inferior cava. Umbilical artery catheters ideally should be located in the high (T6–T9) or low (L3–L5) position, away from major arterial branches. Umbilical venous catheters should be positioned with the tip in the inferior vena cava and not in a hepatic branch.
Bony structures	The skeleton should be evaluated, especially the general configuration of the thoracic cage. Normally, over time, the cephalic portion of the thoracic cage becomes rounded and the transverse diameter increases. Hyperaeration exaggerates cephalic rounding, and the horizontal position of the rib arcs. Hypoaeration reduces the diameter of the upper thorax and increases the inferior slope of the rib arcs (bell-shaped thorax). The radiograph must be evaluated for fractures, dislocations, hypodensities, or other lucencies. Persistent elevation of the scapula and an ipsilateral elevated diaphragm (which occur secondary to phrenic nerve injury) may accompany Erb's palsy. Scans should be done for vertebral, rib, and other bony anomalies. Rib aplasia is associated with hemivertebrae, and complete or partial aplasia of the clavicles may be a manifestation of chromosomal abnormality. The proximal humeri can yield information related to congenital infections such as in rubella, syphilis, and cytomegalovirus infection. The bone density should be evaluated in relation to film penetration.

AP, anteroposterior; NG, nasogastric.

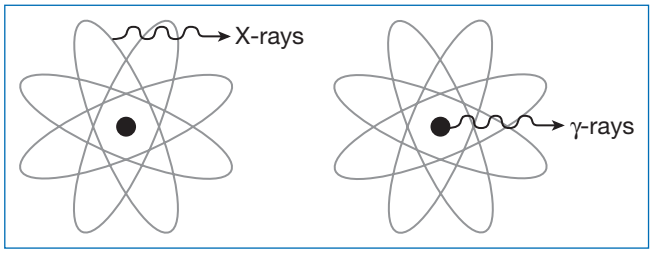

FIGURE I.8 X-rays are produced outside the nucleus of artificially excited atoms; gamma (γ) rays are produced inside the nucleus of radioactive atoms.

radioactive phosphonate agents used for skeletal scanning, and the maximum radiation dose is to the bladder mucosa (Dowd & Tilson, 1999; Treves, 1995). Promoting diuresis can reduce this dose effect. The radiation hazards in radionuclide imaging, therefore, are affected by the physiologic distribution of the agent and its physical half-life, the dose of radionuclide administered, and the pharmacologic half-life in the body (Dowd & Tilson, 1999; Treves, 1995).

Choice of Nucleotide. With nuclear diagnostic imaging, several factors help determine the amount of energy actually deposited in the tissue and may influence the choice of radionuclide. These factors include the following (Dowd & Tilson, 1999; Treves 1995):

- Route of entry
- Fraction of the administered dose that actually reaches the tissue
- Rate of biologic removal of the radionuclide
- Amount of radiation the tissue of interest receives from the portion of the radionuclide deposited in tissues other than the one of interest
- Number of microcuries of radionuclide taken in
- Careful calculation of the average energy of the beta particles emitted, of any ancillary gamma rays emitted, and of any loss of radiation out of the specific tissue
- Metabolic or other factors that might alter the distribution of the radionuclide in various tissues of the human population studied

Estimation of the true dose of energy delivered to a specific tissue by radionuclide exposure, plutonium contamination, or external x-ray exposure, therefore, involves serious technical considerations and requires the efforts of physicists skilled in such measurements.

Nearly all radionuclides used in medicine are artificially produced in nuclear reactors. The most versatile of these compounds is technetium 99m (^{99m}Tc), which has many ideal physical properties, including the following (Dowd & Tilson, 1999; Treves, 1995):

1. It is nontoxic and non-allergenic.
2. It is easily bound to other physiologic compounds.
3. It is relatively inexpensive.
4. It circulates in the blood, and small amounts accumulate in the gastric mucosa, salivary glands, and thyroid tissue.
5. It is excreted primarily in the feces and urine but can also be found in sweat and tears.
6. It does not accumulate in the brain (except in the choroid plexus) unless the blood–brain barrier has been disrupted.
7. It has a short physical half-life (6 hours), long enough for tests to be completed while allowing high initial radio activities to be administered within an acceptable radiation hazard.
8. It emits only gamma photons, which can be detected by the sodium iodide crystals of gamma cameras.

Despite the wide use of technetium, it is not suitable for all investigations, and a number of alternative isotopes are available (Box I.1).

The ideal instrument for detecting the radiation emission of the radionuclide is the gamma camera. With this camera, images are rapidly acquired and dynamic studies are easily performed and quantified. Multiple views from various projections can be obtained. The camera consists of a large crystal of sodium iodide protected by a heavy lead collimator. The shielded crystal is placed over the target organ, and the gamma photons emitted from the body strike it and are converted into light scintillations. The pinhole and converging collimators allow the image to be magnified without loss of resolution. These light scintillations are manipulated electronically to define the distribution and intensity of the radioactivity. The final copy of the image is produced on film or stored on videotape or magnetic disk (Alpen, 1998; Bushong, 2013; Dowd & Tilson, 1999; Treves, 1995).

Because radiopharmaceuticals are rarely organ specific, interference from radioactivity outside the organ of interest is always a factor. Advances in computer processing similar to CT have been developed to eliminate this interfering background data, thereby increasing the accuracy of derived data. Two types of computer-enhanced radionuclide imaging are available: single photon emission computed tomography (SPECT) and PET. Both modalities have significant advantages over conventional planar radionuclide imaging in that (1) the sensitivity and qualification of the distribution and density of radioactivity are much greater; (2) three-dimensional imaging is possible with computer reconstruction; (3) the dose of radionuclide is the same; and (4) artifactual lesions can be eliminated (Bellenger et al., 2000; Bushong, 2001; Lewis et al., 2000; Swischuk, 1995, 2003; Tierney, Varga, Hosey, Grafman, & Braun, 2001; Treves, 1995; Weissleder & Mahmood, 2001).

Single Photon Emission Computed Tomography. With SPECT, a gamma camera is rotated 360° around the infant, and a series of equally spaced, cross-sectional images is obtained and stored in the computer. These images are used to reconstruct a series of cross-sectional slices at right angles to the axis of rotation of the camera. Each cross-sectional slice comprises a series of squares arranged in a matrix. Using a mathematical model, the computer can readily reconstruct these cross-sectional slices in other planes, such as the lateral or coronal plane. The image is then viewed directly from the computer screen or formatted on film. This type of computer-enhanced emission tomography scan uses the standard gamma-emitting radionuclides such as technetium, thallium, gallium, and iodine (Lewis et al., 2000; Treves, 1995).

Positron Emission Tomography. With PET, a different type of radiopharmaceutical, called a positron, is used. Positrons are the same size and shape as electrons but have a positive charge. Typical positrons used in this type of imaging are carbon 11, oxygen 15, and nitrogen 13. Using the metabolic nucleotide from oxygen, carbon, or nitrogen, PET scans create images that depict the "metabolic" function of tissue such as the brain (Bushong, 2013; Dowd & Tilson, 1999; Lin, Laine, & Bergmann, 2001; Treves, 1995; Weissleder & Mahmood, 2001). SPECT is widely available for general use, but PET scanning is available only at large university medical centers with access to a cyclotron, which can produce the short-lived positrons required for this imaging modality. Continued advances in particle physics enhance the development of the technique as a research tool in the study of cerebral blood flow and physiology. The recent substitution of fluorine in the glucose molecule has been very useful in the study of cerebral metabolism in neonates after intracranial hemorrhage (Peterson et al., 2000; Rushe et al., 2001; Swischuk, 2003).

Although this modality is not used frequently in clinical medicine, nurses should understand its potential as a research tool.

Collaborative Care. The care of a neonate undergoing a radionuclide scan requires knowledge about the patient's history and clinical manifestations, the type of nuclear scan requested, and the radiopharmaceutical used. In general, the doses of radiopharmaceuticals are based on the infant's body weight, and the total whole-body irradiation is considerably less than that with a conventional radiograph. The infant poses no radioactivity hazard for the nursing staff or other neonates. Linen, diapers, and body excreta can be disposed of in the usual manner. Nurses should be aware that the radionuclide can concentrate in areas other than the organ of interest so that the proper agents for blocking thyroid iodine uptake can be administered or diuresis can be promoted.

Ultrasonographic Imaging

With neonates, ultrasonography is frequently used in the evaluation and treatment of internal anatomic structures. Unlike conventional radiography, ultrasonography does not involve the emission of ionizing radiation. Instead, sound waves are used to evaluate tissue densities, the movement of tissues, and blood flow (Bushong, 1999, 2013; Martin et al., 2015; Swischuk, 1995, 2003). The images can be recorded on videotape, photographic film, light-sensitive paper, or magnetic disk.

Biophysical Principles. By definition, ultrasound is any sound that has a frequency greater than 20,000 cycles/second (Hz), which exceeds the audible range of human hearing (20–20,000 Hz; Bushong, 2013). Ultrasonography uses high-frequency sound waves (3.5–10 MHz). For echocardiography and Doppler studies, the ultrasound frequencies range in the millions of cycles/second (Bushong, 1999). Ultrasonography has the following advantages as a diagnostic tool (Bushong, 1999, 2013; Martin et al., 2015; Swischuk, 1995, 2003):

1. It emits no ionizing radiation and has no known deleterious somatic or genetic effects; therefore, follow-up examinations may be repeated at will.
2. Ultrasound waves can be directed as a beam.
3. Sound waves obey laws of reflection and refraction.
4. Ultrasound waves are reflected by objects of small size.
5. Ultrasonography can be used in a variety of transverse, longitudinal, sagittal, or oblique planes.
6. Ultrasonography is considerably less costly than either CT or MRI.
7. Ultrasound equipment is easily portable.
8. The examination is relatively painless and well tolerated.
9. Sedation is rarely required.
10. Ultrasonography relies on acoustic impedance of tissue to demonstrate anatomy.
11. Ultrasonography is diagnostically accurate.

The following are the principal disadvantages of ultrasonography (Bushong, 1999, 2013):

1. It is operator dependent.
2. It does not provide as much information on organ function as urography.
3. It has limited value as a screening procedure for "acute abdominal distress"; rather, the examination should focus on a particular area of interest.
4. CT is superior in demonstrating the extent of disease, because ultrasonography demonstrates a smaller area of interest and less anatomic detail.
5. Bone, excessive fat, and gas artifacts adversely affect ultrasonography.

Because of these drawbacks, certain parts of the body, such as the brain, must be imaged through an ultrasound "window," such as the anterior fontanelle. In addition, because sound waves are poorly propagated through a gaseous medium, the transducer must have airless contact with the surface being examined, and parts of the body that contain large amounts of air are difficult to examine.

High-frequency sound passes through the body tissues at a fairly constant speed of approximately 1,500 m/second, or 1.5 mm/μsecond (Bushong, 1999, 2013). Using electronic mechanisms, it is possible to time the passage of an ultrasound impulse to within a fraction of a microsecond so that the distance between an ultrasound transducer and a reflecting interface of tissue can be determined to a fraction of a millimeter. The transducer converts electrical energy into ultrasonographic energy and acts as both the emitter of the initial impulse and the receiver of the reflected impulse.

The velocity of sound wave transmission is the product of the sound frequency and the wavelength. The speed at which sound is transmitted varies, depending on the density and compressibility of the medium (Bushong, 1999, 2013). The velocity of sound transmission is low in a gaseous medium because of the large compressibility and low density of the substance. Sound does not exist in the vacuum of outer space but is readily transmitted through objects of greater density, such as water or metal. This principle can be readily illustrated with the use of a tuning fork. When struck, the tuning fork vibrates and emits sound that can be easily heard. However, when the vibrating tuning fork is placed against the mastoid bone of the cranium, the sound is transmitted to the ear much more readily and is perceived as being louder.

Frequency and wavelength are inversely proportional in ultrasonography (Bushong, 1999, 2013). That is, as the ultrasound frequency increases, the wavelength decreases. The ability to distinguish objects of small size with ultrasonography is directly related to the sound wavelength. High-frequency ultrasonography uses short wavelengths and results in better image resolution than is seen with low-frequency, long-wavelength ultrasonography. This is the case because as the ultrasound frequency increases, the degree of interaction with the conducting medium increases, and absorption of the ultrasound beam is increased. Therefore, at higher ultrasound frequencies, less tissue penetration occurs. For example, ultrasound examinations of the eye typically use frequencies of about 10 MHz, whereas an examination of deep structures of the abdomen uses frequencies of about 2.5 MHz (Bushong, 1999).

The frequency-dependent characteristic of ultrasonography results in its highly directional and collimated nature, which enhances its imaging ability (Bushong, 1999). As the frequency of sound increases, its dispersion from the source is reduced and its transmission becomes more like that of a collimated beam. This becomes apparent when experimenting with a household stereo. The woofers produce a low-frequency bass sound that fills the entire room with sound. A person's perception of these low-frequency sounds does not change, no matter where the person stands in the room. However, the higher frequency sound produced by the tweeters does not disperse as well in the room and can best be heard when the person is positioned directly in front of the speakers. In addition, low-frequency sounds seem at times to penetrate and reverberate in the body, which is not true with higher frequency sounds.

These same principles govern ultrasound transmission through tissue. At higher ultrasound frequencies, the beam becomes more collimated in a forward direction. As the ultrasound frequency is increased, the ability to distinguish small objects increases, but the penetrability of the beam decreases. For these reasons, the highest

frequency transducer is chosen to provide the greatest depth for the tissue or organ images.

Ultrasonography is also useful as a diagnostic imaging method because it is reflected at tissue interfaces. A principle called sonic momentum describes the velocity of sound transmitted through tissue. Sound transmission through different tissues varies with sound velocity, the freedom of motion of the molecules (density), and the sound waves' compressibility. The way sound travels through a tissue is often referred to as the acoustic impedance of that tissue. As a sound wave travels through a homogeneous tissue, it continues in a straight line. When the sound wave reaches an interface between two tissues with different acoustic impedances, it undergoes reflection and refraction (Figure I.9; Bushong, 1999, 2013). The amount of sound reflected depends on the degree of difference between the two tissues; the greater the disparity, the greater the reflection. Diagnostic ultrasound has little interest in the refracted wave but is primarily interested in the intensity of the reflected beam relative to the original sound wave (Bushong, 1999, 2013).

The major patterns of ultrasound reflection are anechoic, echoic, and mixed. An anechoic structure, which is described as sonar lucent, is a structure in which the acoustic medium is homogeneous and the sound waves are unimpeded. An anechoic structure may be fluid filled (bladder), cystic (hydronephrosis), or solid (lymphoma), as long as the tissue is homogeneous. Cystic structures usually have sharp echogenic margins anteriorly and posteriorly. Echoic structures are inhomogeneous and reflect sound waves. These tissues are generally solid and have a variety of densities (typical Wilms' tumor) or may be cystic (hemorrhagic Wilms' tumor). A mixed pattern of reflections has the combined qualities of anechoic and echoic tissues. In addition, ribs and calculi may cause imaging artifacts on an ultrasonographic image. These dense structures prevent further penetration of the ultrasound beam and cause a band-like region of decreased sound transmission beyond that point, called acoustic shadowing (Bushong, 1999).

Applying these principles to clinical practice, it is known that ultrasound is propagated differently in various human tissues and is reflected from each acoustic interface (Bushong, 1999, 2013). A stationary interface results in a reflected ultrasound wave that has the same frequency as the transmitted wave. When the tissue interface is moving (e.g., the movement of red blood cells in a vessel), the reflected ultrasound wave has a shifted frequency directly proportional to the velocity of the reflecting blood cells, in accordance with a principle called the Doppler effect. If the movement of the blood cells is toward the transducer, the frequency of the reflected wave is higher than the transmitted frequency. Conversely, movement of blood away from the transducer results in a lower frequency of the reflected wave (Bushong, 1999, 2013). The difference between the transmitted frequency and the reflected frequency is called the Doppler shift. It is the principle of sound frequency shifts that allows the application of the mathematical relationship between the velocity of the target and the Doppler frequency to calculate flow. This is used most commonly in the echocardiographic evaluation of the heart and in cerebral blood flow determinations (Bushong, 1999, 2013).

Modes of Ultrasonography. Currently, there are five modes of ultrasonic imaging: two static modes (A-mode and B-mode), two dynamic modes (M-mode and real-time), and one Doppler mode. The two static and two dynamic modes use a pulse-echo transducer, which sends ultrasound waves for 0.0001 seconds and then waits for the reflected sound for 0.999 seconds. The first and most intense reflection of a sound wave occurs at the transducer–patient interface. At each succeeding tissue interface, the reflection of the sound wave diminishes in intensity as the tissue is penetrated.

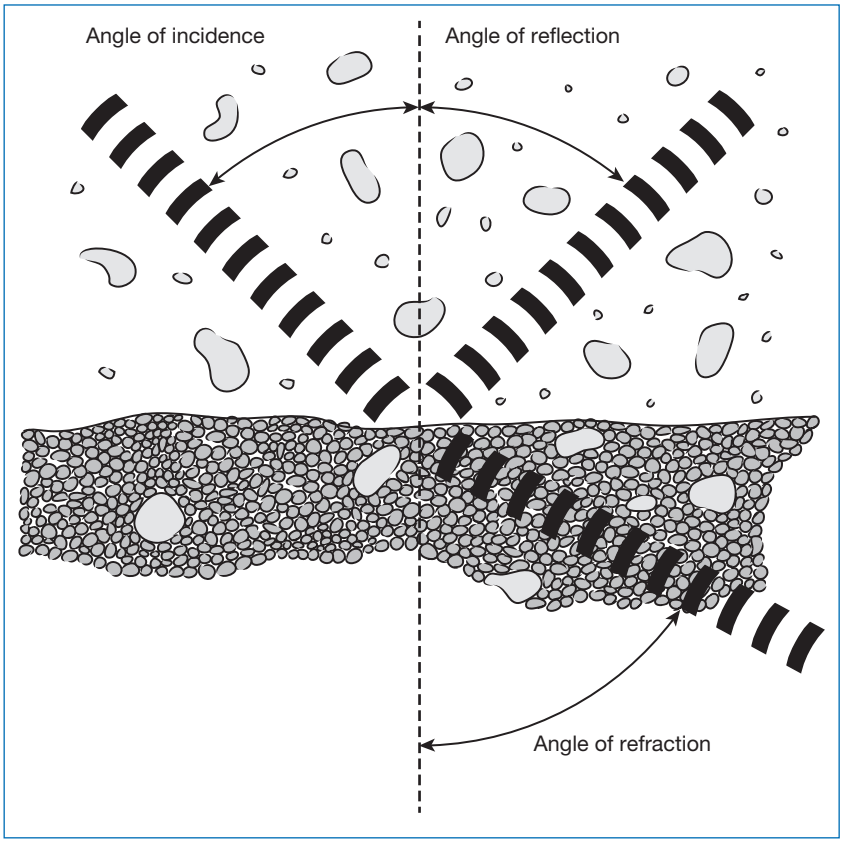

FIGURE I.9 The reflection and refraction of ultrasound.

The time required for the pulse to be reflected to the transducer and its returned intensity indicate the position of the interface; the reflection is indicated as a blip on the video display screen (Bushong, 1999, 2013).

In A-mode, ultrasonic images are displayed on the video screen as a series of vertical blips that represent the returning echoes. The distance between these blips is proportional to the distances between the tissue interfaces, and the height of each blip is proportional to the intensity of the reflected beam. Thus, distal reflections produce lower blips (Bushong, 1999). The main purpose of A-mode imaging is to measure depths of interfaces and to detect their separation accurately. A-mode ultrasonography is primarily used in echoencephalography to determine the cranial midline; it is also used for ultrasonically guided aspiration techniques such as amniocentesis. The advantages of A-mode are that it relies on axial resolution, it is relatively inexpensive, and it is easy to use. The primary disadvantage of this mode is that it requires frequent calibration (Bushong, 1999).

B-mode or brightness-mode ultrasonic imaging displays information as dots, with the brightness of the dot corresponding to the distance of the reflecting interface from the transducer (Figure I.10A and B). Advances in microcomputers and electromechanical coupling have resulted in a compound B-mode image (Bushong, 1999). This is achieved when the spatial position and direction of the ultrasound beam are coupled to the video display screen and the B-mode pulses are individually stored while the transducer is moved about the body. The image that appears on the video display screen, therefore, is the summation of many individual B-mode lines. The spatial resolution of this type of imaging varies considerably and depends on the transducer's characteristics and the electromechanical linkages available commercially. This mode of imaging has become widely used, especially for intracranial and abdominal examinations. The B-mode transducer can be moved linearly to provide a rectangular scan view, or it can be angled to provide a sector scan (Bushong, 1999).

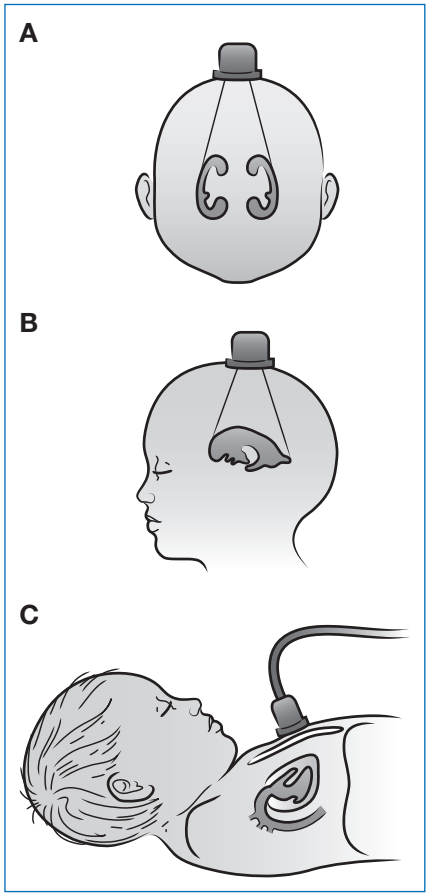

FIGURE I.10 (A) Ultrasound display pattern defining the sagittal sections of ventricular shape and size using brightness (B-mode) imaging. (B) Ultrasound display pattern defining the shape and size of lateral ventricles in the neonate using B-mode imaging. (C) M-mode ultrasound display pattern produces a strip chart for tracing moving tissue interfaces such as appear in the heart.

M-mode, or motion mode, is an imaging process that incorporates pulse-echo ultrasonography to define tissue movement. If an ultrasound transducer is operated in A-mode over the heart, it detects a number of vertical blips from stationary objects, which indicate the motionless interfaces of the tissue. The amplitude of these blips is proportional to the intensity of the echo. The magnitude of the moving objects represents the degree of movement of tissue interface. If this A-mode scan is converted into a B-mode scan, the image is transformed into a number of dots, some of which are fixed and some of which are moving. If this image is driven on the x-axis according to time, as in a chart recording, a tracing of the dots results (Figure I.10C). The stationary dots trace a regular pattern according to the motion of the tissue interface. The y-axis is the depth of the tissue plane. This type of imaging is used primarily to monitor heart function and can be synchronized with the electrocardiograph (Bushong, 1999).

Real-time ultrasonic imaging is another dynamic form of examining tissues. Real time is considered the ultrasonic fluoroscope and has several advantages over B-mode imaging, including the following:

1. Real-time ultrasonography units cost considerably less than B-mode units.
2. Acquisition of real-time images is much less dependent on operator skill.
3. Real-time examinations take less time because the imaging technique is relatively easy.
4. Portable versions of real-time units are readily available.

The transducer used for real-time ultrasonography is longer than the one used for B-mode imaging; therefore, more gel is needed. The real-time transducer is moved over the surface until the anatomic region of interest is found. The dynamic image is recorded on videotape, and the examiner obtains stop-action frames by taking sequential photographs of the display. The disadvantages of real-time ultrasonography are that (1) the ultrasound beam interacts with tissue interfaces from only one direction, whereas B-mode transducers can move while storing the image from many directions, and (2) lateral resolution is superior in B-mode imaging compared with real-time imaging (Bushong, 1999).

The popularity of real-time ultrasonography as an imaging modality has generated three types of real-time transducer devices—mechanical, linear array, and phased array—with displays that have distinct characteristics. The mechanical transducer was the first real-time device developed. This transducer is motorized so that the ultrasound beam is mechanically swept across the field in an oscillating fashion. Each sweep results in one image frame, and as many as 15 frames/second can be obtained. The transducer can be moved linearly for a rectangular view or in an angulated fashion for a sector view (Bushong, 1999). The mechanical transducer was not popular in the early days of real-time ultrasonography because of the limitation of frame rate per second, restricted field of view, and distortion. In recent years, manufacturers have improved this transducer by increasing the frame rate, expanding the viewing field, and reducing the distortion.

The linear array transducer device has a line of 32 transducers aligned in a single case. Because each transducer is only 2 mm

wide, the overall length of the transducer case is 64 mm. In linear array, each transducer is energized in sequence from one to 32. This provides 32 image lines over the pulse of ultrasound, called sequential linear array. If four or five contiguous transducers are energized simultaneously, each pulse of the ultrasound results in four or five scan image lines, called segmental linear array. In a typical system, the transducers are fired in an overlapping pattern so that numbers 1 through 5, then 2 through 6, 3 through 7, and so on, are segmentally, then sequentially energized (Bushong, 1999). This type of transducer device provides for greater image line density and improved image quality over sequential linear array devices. As with the mechanical devices, sequential and segmental linear array devices have poor lateral resolution.

Phased-array real-time ultrasonic imaging is similar to linear array in that it incorporates segmental excitation of the transducer elements. The transducers are segmentally sequenced and have programmable electronic circuitry to incorporate delay lines, so that the excitation and reception of the ultrasound waves by each element can be timed precisely. This delay allows a plane of sound waves from the transducer to be directed, or "phased." The result is a sector scan with a maximum sector angle of 90° (Bushong, 1999). The scan line rate, frame rate, and depth of scan can be selected. The electronic delay lines on the receiver circuitry allow some depth of focusing through synchronization of the returning reflected pulses. The transducer size is smaller than with linear array, and axial resolution is good. As with real-time imaging, lateral resolution is poor but can be improved with acoustic focusing.

Biologic Effects of Ultrasonography. Ultrasonic imaging was introduced into obstetric practice in 1966. Since that time, despite the widespread use of this imaging modality and the use of multiple scans during an individual pregnancy, there have been no reports of manifested injury or late effects in human beings (or fetuses) exposed to diagnostic levels of medical ultrasound (Bushong, 1999). In the laboratory, however, it has been shown that much higher levels of ultrasound can produce measurable tissue effects. The levels of ultrasound energy required to produce these effects are approximately 1,000 times greater than those used in diagnostic medical ultrasonography. In vitro, the mechanism of action of the ultrasonic effects on tissue is presumed to be increased tissue temperature, cavitation, and various viscous stresses on the tissue (Bushong, 1999, 2013).

The thermal effects of ultrasonography occur because of the molecular agitation and relaxation processes caused by the passing sound waves (Bushong, 1999, 2013). Extremely high levels of ultrasound are required to produce even a measurable increase in tissue temperature. The effects of the elevation in tissue temperature occur not only with ultrasonography but also with fever or hyperthermia. At the local tissue level, significant changes in tissue temperature, regardless of the cause, result in structural changes in macromolecules and membranes and alter the rates of biochemical reactions. The thermal effects of diagnostic medical ultrasonography do not result in any increase in tissue temperature.

High levels of experimental ultrasound can also result in alteration in the structure and function of macromolecules and cells without an increase in tissue temperature. These changes can result from cavitation, which occurs when tiny bubbles of gas are formed during the molecular relaxation after sound wave agitation (Bushong, 1999, 2013). As the cavitation increases, more energy is absorbed from the incident ultrasound beam. This is thought to cause a disruption of molecular bonds and the production of free hydrogen and hydroxide radicals resulting from the dissociation of water vapor. Cavitation effects have not been observed with the levels of sound used in diagnostic medical ultrasonography (Bushong, 2013).

Every tissue has a specific density, and the density of tissues on either side of an interface may not be equal. As ultrasound waves interact along this tissue interface, the differences in density result in stress exerted on the tissue boundary. This tissue boundary stress results in small-scale fluid motions called microstreaming (Bushong, 1999). It is theoretically possible that microstreaming can disrupt membranes and cells in the region of the interface. Microstreaming has been observed in vitro only after exposure to extremely high levels of ultrasound.

Experimental evidence has shown that ultrasound in sufficiently high doses can degrade macromolecules and may produce chromosomal aberrations and cause cellular death. To induce these effects in living tissue, however, ultrasound intensities of 10 W/cm^2 exposure over considerable periods of time are necessary. The absolute minimum dose level that has been reported to have an observable effect in experimental specimens is 100 mW/cm^2, and even then only after many hours of continuous ultrasonographic application (Bushong, 1999, 2013). The intensity range of diagnostic ultrasound is 1 to 10 mW/cm^2, and examinations using this modality frequently require only a few minutes of ultrasound exposure. There are no reports of human chromosomal effects or of changes in prenatal or neonatal death rates after exposure to ultrasound, nor is there evidence that ultrasound induces latent malignant disease. Thus, the use of ultrasonic imaging has grown in all areas of medicine, and its uses in neonatal care are increasing rapidly.

Indications for ultrasonography in neonatal intensive care commonly include evaluation of brain parenchyma and ventricular size, myocardial function and structure, cholelithiasis, choledochal cysts, intestinal duplication, renal neoplasms, urinary tract dilation and duplication, pelvic masses, and skeletal anomalies of the spine and hips (Martin et al., 2015).

Collaborative Care. The care of a neonate undergoing a diagnostic ultrasound examination ensures that any disruption of the infant's microenvironment is minimal. The infant's temperature can be maintained more easily if the ultrasound examination can be performed by using the transducer in the incubator. Although this method is technically more cumbersome for the ultrasonographer, cooperation between the ultrasonographer and the nurse facilitates the procedure. The transducer gel should be warmed to the same temperature as the infant's incubator to minimize heat loss. Heat loss caused by wet blankets or skin can be reduced by placing a diaper or some other pad under the imaged area, as well as by removing the gel quickly and drying the skin after the scan.

Having an understanding of the imaging examination to be performed allows the nurse to more accurately position the infant and move electrodes, tape, or other artifacts that limit the surface area to be scanned. The nurse's assistance in performing an ultrasound examination is important for monitoring the infant's tolerance of the procedure and for providing information that may be of diagnostic importance to the ultrasonographer. In addition, the nurse's presence at the bedside allows for immediate visual feedback and interpretation of the extent of the pathologic condition that may be present. This knowledge enables the nurse to better support the infant's parents as they make decisions on further diagnostic testing and treatment after their discussions with the medical staff. Interaction with the ultrasonographer at the bedside may also help the nurse to anticipate the infant's immediate and long-term future healthcare needs.

Magnetic Resonance Imaging

The theoretic basis for MRI is a development of research conducted since the 1940s for studying atomic nuclear structure, which resulted in the awarding of the Nobel Prize for physics in 1952 to

Edward Purcell and Felix Block. In addition to the advances in atomic nuclear research, other developments were necessary, such as superconductivity and advances in computer programming, before this concept could be applied to diagnostic imaging.

As an imaging modality, MRI has several advantages over CT and ultrasound (Bushong, 2003, 2013; Huda, Chamberlain, Rosenbaum, & Garrisi, 2001; Lansberg, O'Brien, Tong, Moseley, & Albers, 2001; Peled & Yeshurun, 2001; Schierlitz et al., 2001):

1. Like ultrasonography, MRI does not use ionizing radiation to produce the image, but rather uses magnetic fields and radio waves.
2. The magnetic resonance image depends on three separate molecular parameters that are sensitive to changes in structure and bioactivity rather than on x-ray photon interaction with tissue electrons as in CT.
3. The region of the body imaged with MRI is not limited by the gantry geometry, as it is with CT, but can be controlled electronically, allowing imaging in transverse planes and in true sagittal, coronal, and oblique planes.
4. Magnetic resonance images are free of the high-intensity artifacts produced in CT scans by sharp, dense bone or metallic surgical clips.

The principal disadvantages of MRI are its high cost and limited availability. Its use for clinically unstable infants on life support is also restricted because the strong magnetic field can interfere with monitoring devices, and access to the infant is limited during the procedure (Lansberg et al., 2001; Peled & Yeshurun, 2001; Schierlitz et al., 2001; Swischuk, 1995, 2003).

Despite the disadvantages of MRI, its clinical applications are rapidly expanding. The image quality is excellent, with the advances in the use of surface coils, and more sensitive head and body coils allow structures such as cranial nerves and small joints to be evaluated more precisely. The increased use of gating, fast scanning, and diffusion-weighted and magnetization transfer imaging have improved MRI evaluation of many tissues and structures and have identified many pathologic conditions that previously could not be quantified (Bushong, 2001; Fogel, Rychik, Chin, Hubbard, & Weinberg, 2001; Huppi et al., 2001; Nolte, Finsterbusch, & Frahm, 2000; Sinson et al., 2001; Swischuk, 1995).

Biophysical Principles. All particles in an atom have either a positive or a negative charge, or a "spin," like a tiny spinning top. The total spin of the protons and neutrons on the nucleus is the sum of the individual spins. Moving charges create magnetic fields; thus, the nucleus of an atom develops north and south magnetic dipoles (Bushong, 2003, 2013; Dowd & Tilson, 1999; Juhl et al., 1998). In most materials such as soft tissue, these little spinning magnetic dipoles are randomly oriented (Figure I.11A). This random orientation causes all the spins and magnetic forces to cancel in the material so that the net magnetic force is zero. However, if the material is placed in a strong magnetic field, the magnetic dipoles align themselves, much like a compass needle aligns itself with the Earth's magnetic field. The alignment of these magnetic dipoles produces a net magnetic force or vector that is oriented parallel to the direction of the imposed magnetic field (Figure I.11B). Not all magnetic dipoles become aligned; some are in constant thermal motion so that nuclei are continually knocked out of alignment (Bushong, 2003, 2013; Juhl et al., 1998).

In MRI, the strong magnetic field is imposed to align the molecular magnetic dipoles, and radio frequency pulses are then applied. The known specific frequency of these radio waves displaces the net magnetic moment by an amount determined by the strength and duration of the pulse. The frequency is directly proportional to the strength of the magnetic field and is known as the resonant

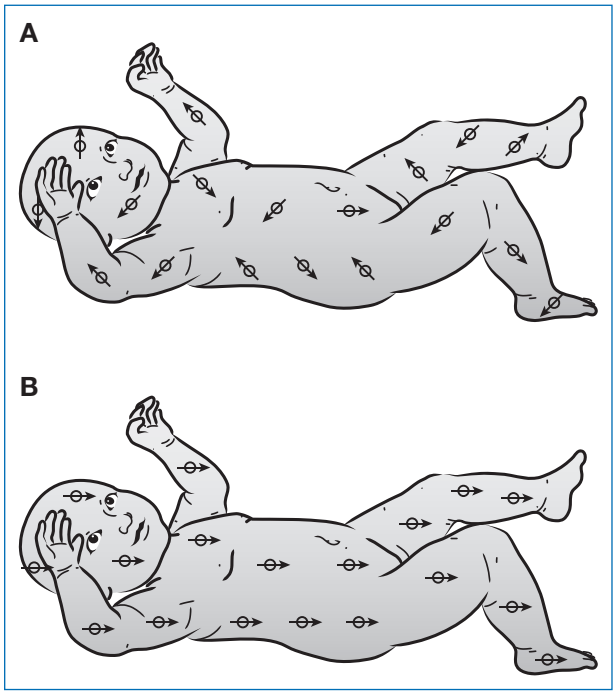

FIGURE I.11 (A) All the magnetic moments are randomly oriented in the body so that the net magnetic charge is zero. (B) Applied radio frequency pulses align the magnetic moments along a predetermined axis. The rate at which the atoms return to their "normal" magnetic moment after the radio frequency is stopped is characteristic for physiologic and pathologic tissues and is responsible for creating the magnetic resonance image.

frequency. After the pulse, the protons emit radio frequencies as they return to their original orientation. Therefore, the frequency of signals emitted by the protons after the application with radio frequency waves reflects their position in the tissue. Although in theory any stable nuclei can be used, hydrogen is the most abundant and has the strongest resonance (Bushong, 2003, 2013; Juhl et al., 1998).

When protons are placed in a magnetic field, proton alignment does not occur instantaneously but rather increases exponentially with a time constant characterized by T_1, or spin–lattice relaxation time, which reflects the interaction of the hydrogen nucleus with its molecular environment (Bushong, 2003, 2013; Juhl et al., 1998). T_1 characterizes the return of the net magnetization from its displaced position to its normal vertical position resulting from spin–lattice interactions. To form an image, the radio frequency pulses must be applied repetitively. After each radio frequency pulse, the net magnetic force of the sample is reduced; therefore, too rapid a radio frequency repetition depletes the magnetization of the tissue, and an image cannot be produced. Thus, radio frequency pulses are sequenced with a certain time interval to allow the magnetic force to be reestablished. The longer the time interval, the greater the magnetic force and the longer the imaging time required (Bushong, 2003, 2013; Juhl et al., 1998).

After exposure to the radio frequency pulse has occurred, the signal emitted from the sample of protons decays exponentially with a time constant referred to as T_2, or spin–spin relaxation time. T_2 reflects the magnetic interactions between protons. It characterizes the exponential loss of signal caused by dephasing or desynchronization of magnetic force, which results from spin–spin interactions (Bushong, 2003, 2013; Dort et al., 2001; Juhl et al., 1998). The interval between the application of a radio frequency pulse and the emitted signal depends on the alignment and synchronization of magnetic dipoles. A strong magnetic force results

in a long interval for the emitted signal after the pulse; this explains the contrast between tissues with different values of T_2 changes. T_1 is not equal to T_2, because each nucleus is not located within identical magnetic fields. Each hydrogen nucleus is subject to different local magnetic fields because of the presence or absence of other hydrogen nuclei (Bushong, 2003, 2013; Dort et al., 2001).

The third variable that affects image resolution with MRI is spin density. Spin density refers to the strength of the signal received from the nuclei before any of the decay processes have taken place (Bushong, 2003, 2013; Dort et al., 2001; Juhl et al., 1998). This strength is proportional to the number of nuclei within the detection volume of the scanner. Spin density is an indication of hydrogen concentration in the tissue.

A magnetic resonance image results from the mixture of these three properties (T_1, T_2, and spin density) unique to each tissue. The values of T_1 and T_2 for various tissues have been defined. A wide range of values exists among various types of tissue, and considerable differences have been documented between pathologic and normal tissue (Dort et al., 2001; Juhl et al., 1998). Each number defined for the relaxation times (T_1 and T_2) for various tissues depends on the primary external magnetic field and thus may vary from scanner to scanner. The visual projection of the magnetic resonance image is similar to that obtained in CT. By controlling the gradient field of radio frequency pulses, a series of projections at uniform angles through the tissue can be collected. The computer can then reconstruct the image and can emphasize the individual T_1, T_2, or spin density parameters to further define detail (Bushong, 2003, 2013; Dort et al., 2001; Juhl et al., 1998).

The spatial resolution of an MRI scan compares favorably with that of CT. If the object scanned is of high tissue contrast, a lesion as small as 1 mm can be defined. As more data is collected on this imaging modality, even greater spatial resolution and enhanced three-dimensional images are being obtained. As stronger magnetic fields are used, the emitted signals become stronger, and greater resolution may be possible using even higher radio frequency pulses (Bushong, 2003, 2013; Dort et al., 2001).

MRI is better able than CT to detect differences between low-contrast structures. The difference in T_1 and T_2 MRI between biologic tissues is frequently 10% or more. For example, on CT scans, the x-ray photon attenuation coefficient between gray and white matter is approximately 0.5%, whereas the differences in T_1, T_2, and spin density between gray and white matter are great, allowing for more accurate definition of these two tissues (Bushong, 2003, 2013; Dort et al., 2001). Thus, MRI has become the diagnostic imaging mode of choice for certain neurologic conditions such as multiple sclerosis, cerebral infarctions, and periventricular leukomalacia. MRI may be useful in the early diagnosis of periventricular leukomalacia, before the characteristic cystic lesions have developed (Huppi et al., 2001; Krishnamoorthy, Soman, Takeoka, & Schaefer, 2000; Peterson et al., 2000; Sie, Barkhof, Lafeber, Valk, & van der Knaap, 2000; Tierney et al., 2001).

Safety of Magnetic Resonance Imaging. MRI scanning uses three kinds of fields associated with the imaging process: (1) a static, moderately strong magnetic field; (2) a switched, weaker magnetic field gradient; and (3) radio frequency waves. The energies associated with the imaging process are approximately 10^{-8} eV/quantum, which are too weak to cause ionization or breakage of chemical bonds (Bushong, 2003, 2013; Dowd & Tilson, 1999). Energies associated with body temperature elevations are 100,000 to 1 million times greater; therefore, these temperature effects are far more disruptive to chemical bonds than the energy associated with MRI (Bushong, 2003, 2013).

In the laboratory, biologic responses in animals, chromosomes, plant seeds, and molecular specimens have shown effects only after extremely high intensities of MRI energy. Long-term studies of human beings exposed to radio frequency waves have not demonstrated any deleterious effects (Bushong, 2003, 2013; Dowd & Tilson, 1999).

The hazards of MRI relate primarily to any ferromagnetic objects (e.g., tools, oxygen cylinders, watches, bank cards, pens, and paper clips) that are accelerated toward the center of the magnetic field. The magnetic propulsion of these objects can result in projectile damage; therefore, any patient with a pacemaker or an extensive metal prosthesis should be excluded from this imaging technique. In addition, MRI has not been fully tested with pregnant women.

Collaborative Care. The care of a neonate who requires an MRI scan includes careful preparation and elimination of any ferromagnetic objects brought near the magnetic field. The infant's condition must be clinically stable because the strong magnetic field affects some monitoring devices, and visualization of the neonate is impossible during the scan. Surface respiratory monitors and possibly an esophageal stethoscope may be used. An MRI scan is degraded by motion; therefore, the infant must be positioned comfortably and safely in the magnetic cylinders. Because the infant must remain motionless for several minutes, an MRI scan is best done after the infant has been fed and is sleeping. If the infant is unable to remain motionless for the duration of the scan, oral chloral hydrate sedation may be recommended.

LABORATORY VALUES

A wide variety of laboratory tests can be used in both the diagnosis and care of the newborn. The values given in this chapter represent the broader normal ranges, but values in a specific chapter may vary slightly, depending on the range the author considers to be within normal limits. Every attempt has been made to provide consistent diagnostic and laboratory values. However, many hospitals have compiled their own lists of acceptable laboratory test values; therefore, specific laboratories should be contacted when evaluating results (Tables I.3–I.16).

CARDIAC PROCEDURES

Electrocardiography

Electrocardiography is a noninvasive diagnostic tool used with neonates. It is most useful in the diagnosis and management of cardiac arrhythmias or in conjunction with other diagnostic measures to evaluate cardiac function, specifically the circulatory demands placed on individual heart chambers. In the neonatal period, however, electrocardiography is less helpful in evaluating cardiac anomalies associated with significant ventricular enlargement (Flanagan, Yeager, & Weindling, 2015).

Echocardiography

Echocardiography, another noninvasive diagnostic procedure, is commonly used in the evaluation of the structure and function of the heart. This information can be important not only in the preoperative assessment of cardiac defects but also in the postoperative evaluation of procedures. High-frequency sound waves send vibrations to the structures in the heart, which reflect energy, which is transmitted into a visual image. Echocardiography may be used prenatally as early as 11 weeks' gestation when used transvaginally or 18 weeks' gestation when used transabdominally (Erenberg, 2011).

Single dimension echocardiography allows the evaluation of anatomic structures, including valves, chambers, and vessels.

TABLE I.3

COMMON ELECTROLYTE AND CHEMISTRY VALUES

Parameter	Normal Value
Serum Electrolytes	
Sodium (Na)	135–145 mEq/L
Potassium (K)	4.5–6.8 mEq/L
Chloride (Cl)	95–110 mEq/L
Carbon dioxide (CO_2)	20–25 mmol/L
Serum Chemistries	
Blood urea nitrogen (BUN)	6–30 mg/dL
Calcium (Ca)	7–10 mg/dL
Creatinine (Cr)	0.2–0.9 mg/dL
Glucose (G)	40–97 mg/dL
Magnesium (Mg)	1.5–2.5 mg/dL
Phosphorus (P)	5.4–10.9 mg/dL

TABLE I.4

NORMAL HEMATOLOGIC VALUES

	Gestational Age (Weeks)		Full-Term Cord Blood	Day 1	Day 3	Day 7	Day 14
Hemoglobin (g/dL)	28	34	16.8	18.4	17.8	17	16.8
Hematocrit (%)	14.5	15	53	58	55	54	52
Red cells (mm^3)	45	47	5.25	5.8	5.6	5.2	5.1
MCV (μm^3)	4	4.4	107	108	99	98	96
MCH (pg)	120	118	34	35	33	32.5	31.5
MCHC (%)	40	38	31.7	32.5	33	33	33
Reticulocytes (%)	31	32	3–7	3–7	1–3	0–1	0–1
Platelets ($\times 10^3/mm^3$)	5–10	3–10	290	192	213	248	252

MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume.

Source: Adapted from Klaus, M. H., & Fanaroff, A. A. (Eds.). (2001). *Care of the high-risk neonate* (5th ed.). Philadelphia, PA: WB Saunders.

TABLE I.5

WHITE CELL AND DIFFERENTIAL COUNTS IN PREMATURE INFANTS

	Birth Weight					
	Under 1,500 g			**1,500–2,500 g**		
	1 Week Old	**2 Weeks Old**	**4 Weeks Old**	**1 Week Old**	**2 Weeks Old**	**4 Weeks Old**
Total Count (× 10^3/mm^3)						
Mean	16.8	15.4	12.1	13	10	8.4
Range	6.1–32.8	10.4–21.3	8.7–17.2	6.7–14.7	7.0–14.1	5.8–12.4
Percentage of Total Polymorphs						
Segmented	54	45	40	55	43	41
Unsegmented	7	6	5	8	8	6
Eosinophils	2	3	3	2	3	3
Basophils	1	1	1	1	1	1
Monocytes	6	10	10	5	9	11
Lymphocytes	30	35	41	9	36	38

Source: Adapted from Klaus, M. H., & Fanaroff, A. A. (Eds.). (2001). *Care of the high-risk neonate* (5th ed.). Philadelphia, PA: WB Saunders.

TABLE I.6

SUMMARY OF NORMAL URINARY LABORATORY VALUES

	Age of Infant	**Normal Value**
Ammonia	2–12 months	4–20 μEq/min/m^2
Calcium	1 week	Under 2 mg/dL
Chloride	Infant	1.7–8.5 mEq/24 hours
Creatinine	Newborn	7–10 mg/kg/day
Glucose	Preterm	60–130 mg/dL
	Full-term	12–32 mg/dL
Glucose (renal threshold)	Preterm	2.21–2.84 mg/mL
	Full-term	2.20–3.68 mg/mL

(*continued*)

TABLE I.6

SUMMARY OF NORMAL URINARY LABORATORY VALUES (*continued*)

	Age of Infant	Normal Value
Magnesium		180 ± 10 mg/1.73 m^2/dL
Osmolality	Infant	50–600 mOsm/kg
Potassium		26–123 mEq/L
Protein		Under 100 mg/m^2/dL
Sodium		0.3–3.5 mEq/dL (6–10 mEq/m^2)
Specific gravity	Newborn	1.006–1.008

Source: Adapted from Ichikawa, I. (Ed.). (1990). *Pediatric textbook of fluids and electrolytes.* Baltimore, MD: Lippincott Williams & Wilkins.

TABLE I.7

ELECTROCARDIOGRAPHIC DATA PERTINENT TO THE NEONATE

	Age			
Parameter	**Birth to 24 Hours**	**1–7 Days**	**8–30 Days**	**1–3 Months**
Heart rate (beats/minute)	119 (94–145)	133 (100–175)	163 (115–190)	154 (124–190)
PR interval (seconds)	0.1 (0.07–0.12)	0.09 (0.0 7–0.12)	0.09 (0.07–0.11)	0.1 (0.07–0.13)
P wave amplitude II	1.5 (0.8–2.3)	1.6 (0.8–2.5)	1.6 (0.08–2.4)	1.6 (0.8–2.4)
QRS duration (seconds)	0.065 (0.05–0.08)	0.06 (0.04–0.08)	0.06 (0.04–0.07)	0.06 (0.05–0.08)
QRS axis (°)	135 (60–180)	125 (80–160)	110 (60–160)	80 (40–120)
R amplitude V_{4R} (mm)	8.6 (4–14.2)	—	6.3 (3.3–8.5)	5.1 (1.1–10.1)
R amplitude V_1 (mm)	11.9 (4.3–21)	—	11.1 (3.3–18.7)	11.2 (4.5–18)
R amplitude V_5 (mm)	10.2 (4–18)	10.7 (3.4–19)	11.9 (3.5–27)	13.6 (7.3–20.7)
R amplitude V_6 (mm)	3.3 (2.3–7)	5.1 (2.2–13.1)	6.7 (1.7–20.5)	8.4 (3.6–12.9)
S amplitude V_{4R} (mm)	3.8 (0.2–13)	—	1.8 (0.8–4.6)	3.4 (0–9.3)
S amplitude V_1 (mm)	9.7 (1.1–19.1)	—	6.1 (0–15)	7.5 (0.5–17.1)
S amplitude V_5 (mm)	11.9 (0.24)	6.8 (3.6–16.2)	4.8 (2.7–12.3)	4.7 (2–12.7)
S amplitude V_6 (mm)	4.5 (1.6–10.3)	3.3 (0.8–9.9)	2 (0.6–9)	2.4 (0.8–5.8)

Sources: Adapted from Fanaroff, A., & Martin, R. (Eds.). (1987). *Neonatal-perinatal medicine: Diseases of the fetus and infant* (4th ed.). St. Louis, MO: Mosby; Liebman, J., & Plonsey, R. (1977). Electrocardiography. In A. J. Moss, F. H. Adams, & G. C. Emmanouilides (Eds.), *Heart disease in infants, children and adolescents* (2nd ed.). Baltimore, MD: Lippincott Williams & Wilkins.

TABLE I.8

ACID–BASE STATUS

Determination	Sample Source	Birth	1 Hour	3 Hours	24 Hours	2 Days	3 Days
Vigorous Term Infants (Vaginal Delivery)							
pH	Umbilical artery	7.26					
	Umbilical vein	7.29					
Pco_2 (mmHg)	Arterial	54.4	38.8	38.3	33.6	34	35
	Venous	42.8					
O_2 saturation	Arterial	19.8	93.8	94.7	93		
	Venous	47.6					
pH	Left atrial		7.30	7.34	7.41	7.39	7.38
CO_2 content (mEq/L)	—	—	20.6	21.9	21.4	Temporal artery	Temporal artery
Premature Infants							
	Capillary (skin puncture)						
pH	<1,250 g				7.36	7.35	7.35
Pco_2 (mmHg)					38	44	37
pH	>1,250 g				7.39	7.39	7.38
Pco_2 (mmHg)					38	39	38

CO_2, carbon dioxide; O_2, oxygen; Pco_2, partial pressure of carbon dioxide; pH, hydrogen ion concentration.

Source: Adapted from Schaffer, A. J. (1971). *Diseases of the newborn* (3rd ed.). Philadelphia, PA: WB Saunders.

TABLE I.9

SELECTED CHEMISTRY VALUES IN PRETERM AND FULL-TERM INFANTS

Constituent	Preterm Infant	Full-Term Infant
Alkaline phosphatase (U/L; mean ± SD)[a]	207 ± 60 to 320 ± 142	164 ± 68
Ammonia (mcg/dL)[b]		90–150
Base, excess (mmol/L)[b]		−10 to −2
Bicarbonate, standard (mmol/L)[c]	18–26	20–26
Bilirubin, total (mg/dL)		

(*continued*)

TABLE I.9

SELECTED CHEMISTRY VALUES IN PRETERM AND FULL-TERM INFANTS (*continued*)

Constituent	Preterm Infant	Full-Term Infant
Cord[c]	Under 2.8	Under 2.8
24 hours old	1–6	2–6
48 hours old	6–8	6–7
3–5 days old	10–12	4–6
1 month or older	Under 1.5	Under 1.5
Bilirubin, direct (mg/dL)[c]	Under 0.5	Under 0.5
Calcium, total (mg/dL), week 1[d,e]	6–10	8.4–11.6
Ceruloplasmin (mg/dL)[b]		1–3 months: 5–18
Cholesterol (mg/dL)		
Cord[c]		45–98
3 days to 1 year old		65–175
Creatine phosphokinase (U/L)		
Day 1[f]		44–1,150
Day 4		14–97
Creatine (mg/dL)	10 days: 1.3 ± 0.07	1–4 days: 0.3–1
	1 month: 0.6 ± 0.05	Over 4 days: 0.2–0.4
Ferritin (mcg/dL)		
Neonate[b]		25–200
1 month old		200–600
2–5 months old		50–200
Over 6 months old		7–142
Gamma-glutamyl transferase (U/L)[g]		14–131
Glucose (mg/dL)		
Under 72 hours old[h,i]	20–125	30–125
Over 72 hours old	40–125	40–125

(*continued*)

TABLE I.9

SELECTED CHEMISTRY VALUES IN PRETERM AND FULL-TERM INFANTS (*continued*)

Constituent	Preterm Infant	Full-Term Infant
Lactate dehydrogenase (U/L)[g]		357–953
Magnesium (mg/dL)[e]		1.7–2.4
Osmolality (mOsm/L)[b]		275–295 (may be as low as 266)
Phosphorus (mg/dL)		
Birth[e]		4.5–8.7
Day 5		4.2–7.2
1 month old		4.5–6.5
Aspartate aminotransferase (U/L)[h]		24–81
Alanine aminotransferase (U/L)[h]		10–33
Triglycerides (mg/dL)[c]		10–140
Urea nitrogen (mg/dL)[b]	3–25	4–12
Uric acid (mg/dL)[c]		3–7.5
Vitamin A (mcg/dL); (mean ± SD); (under 10 mcg/dL indicates very low hepatic vitamin A stores)[j]	16 ± 1	23.9 ± 1.8
Vitamin D		
25-Hydroxycholecalciferol (ng/mL)[k,l,m]		20–60
1,25-Dihydroxycholecalciferol (pg/mL)[k,l,m]		40–90

[a] Glass, Hume, Hendry, Strange, and Forfar (1982); [b] Tietz (1988); [c] Wallach (1983); [d] Meites (1975); [e] Nelson, Finnstrom, and Larsson (1987); [f] Drummond (1979); [g] Statlan et al. (1978); [h] Cornblath and Schwartz (1976); [i] Heck and Erenberg (1987); [j] Shenai, Chytil, Jhaveri, and Stahlman (1981); [k] Cooke et al. (1990); [l] Lichtenstein, Specker, Tsang, Mimouni, and Gormley (1986); [m] Serum levels are affected by race, age, season, and diet.

Source: Adapted from Fanaroff, A., & Martin, R. (2002). *Neonatal-perinatal medicine: Diseases of the fetus and infant* (7th ed.). St. Louis, MO: Mosby.

Two-dimensional echocardiography provides more in-depth information about the relationships between the heart and the great vessels (Flanagan et al., 2015).

Doppler echocardiography is used in various forms in the evaluation of characteristics of blood flow through the heart, valves, and great vessels. It can measure not only cardiac output but also flow velocity changes, as demonstrated in stenotic lesions. Regurgitation through insufficiently functioning valves can also be identified. Doppler studies can be used to show regurgitation through insufficiently functioning valves or to identify shunting, as through a patent ductus arteriosus (Bansal, 2015).

Cardiac Catheterization

Historically, cardiac catheterization in the neonate was used for the diagnosis of congenital heart disease. With the advent of more sophisticated echocardiography, especially Doppler echocardiography, cardiac catheterization is used increasingly as a therapeutic modality. The use of radiopaque dye allows for clarification of congenital heart disease and helps to provide data that cannot be obtained from echocardiography.

Immobilization and constant monitoring of the neonate are required during cardiac catheterization. The infant must be

restrained to maintain supine positioning. Electrocardiographic electrodes must also be placed to provide constant monitoring of vital signs. Sedation may be considered to maintain proper positioning during the procedure.

A local anesthetic is administered at the insertion site. A radiopaque catheter is inserted into an arm or leg vessel by percutaneous puncture or cut-down. Under fluoroscopy, the catheter is visualized and passed into the heart. Contrast medium is injected through the catheter to allow visualization of the various cardiac structures. Selected chambers and vessels of the heart can be evaluated for size and function. Intracardiac pressures and oxygen saturations can also be measured during this procedure. The use of balloons during catheterization can facilitate procedures such as septostomy, angioplasty, and valvuloplasty (Erenberg, 2011; Flanagan et al., 2015).

After the necessary information has been obtained, the catheter is carefully removed. If a cut-down was performed, the vessel is ligated and the skin is sutured. Pressure should be applied over a percutaneous puncture site to enhance clot formation. For continued bleeding problems, pressure dressings may be applied to the insertion site; these must be checked frequently for active bleeding. After cardiac catheterization, the vital signs should be measured frequently and compared with precatheterization baseline values. Evaluation of localized bleeding or of signs of hypotension resulting in changes in heart rate and blood pressure is essential. Assessment of the insertion site and affected extremity for bleeding, color, peripheral pulses, temperature, and capillary refill should continue for at least 24 hours after the procedure. In addition, the nurse must monitor for complications of catheterization, including hypovolemia (as a result of bleeding or fluid loss during the procedure), infection, thrombosis, or tissue necrosis.

GENETIC TESTING

Chromosome Analysis

High-Resolution Karyotyping and Banding. Analysis of chromosome composition can assist in the identification of various genetic disorders. A blood specimen is obtained from the infant and used to harvest an actual set of chromosomes. During active cell division, usually during metaphase, the chromosomes are photographed and then arranged in pairs by number. The chromosomes are also separated into regions, bands, and subbands. The end result, a karyotype with banding, is evaluated for the appropriate number of pairs, chromosome size, and structure. Specific genetic disorders can be associated with abnormal numbers of chromosomes (e.g., trisomy 21) or an abnormal chromosome structure, as in cri du chat syndrome, which reflects the loss of part of the short arm of chromosome 5 (Kuller & Cefalo, 1996). Abnormal genes on the chromosomes can also cause genetic disorders, such as Duchenne muscular dystrophy, an X-linked recessive disorder.

High-resolution karyotype is widely used for infants with multiple congenital anomalies. This test consists of analysis of chromosomes from white blood cells. The cells are cultured, stimulated to divide, and cell division is halted with a mitotic inhibitor in the prometaphase stage. In this stage the chromosomes are at their longest length and the observed stained bands can reach 800 to 900. This test can take up to 2 weeks (Gomella et al., 2013).

Fluorescence in Situ Hybridization. Chromosomes can be further analyzed using fluorescence in situ hybridization (FISH) to detect syndromes that are not visible to the naked eye. The FISH process allows fluorescent-coated DNA probes to detect submicroscopic chromosomal deletions. It can be used with interphase and metaphase cells. This test is faster than high-resolution karyotyping (it still could take up to several weeks to complete). This test can provide a quick diagnosis to infants with trisomy 13, 18, 21, or Turner syndrome (Bajaj & Gross, 2015; Gomella et al., 2013; Martin et al., 2015; McLean, 2015).

Bone marrow cells may be analyzed for chromosomes if a more rapid evaluation is required. Skin fibroblast analysis is required when an infant has been transfused, making lymphocyte analysis inaccurate. In cases such as stillbirth, tissue biopsy specimens can be used for chromosome testing because viable lymphocytes are absent (Hamilton & Wynshaw-Boris, 2009).

Sweat Chloride Test

The sweat chloride test is used to evaluate for and confirm the diagnosis of cystic fibrosis. During the procedure the skin is stimulated with pilocarpine and a small electrical current for 5 minutes. The sweat is collected on a 2 × 2-inch gauze pad or filter paper for 30 minutes. Over this 30-minute period, 75 mg of sweat must be produced to ensure an appropriate sweat rate (National Committee for Clinical Laboratory Standards, 1994). A sweat chloride level below 40 mEq/L is normal. Levels between 60 and 165 mEq/L are considered diagnostic for cystic fibrosis (Wilford & Taussig, 1998). Sweat tests can be inaccurate if an inadequate amount of sweat is produced, if the sweat evaporates, or if the patient has edema.

Comparative Genomic Hybridization or Chromosomal Microarray Analysis

The comparative genomic hybridization (CGH) or chromosomal microarray analysis (CMA) detects chromosomal deletions or duplication; this cytogenetic technique is relatively new. CGH/CMA compares reference standard DNA to the patient's DNA through a fluorescent technique. This test compares hundreds of regions across the entire genome to assess for the number of differences. It commonly assesses for microdeletion and microduplication, subtelomeric, and pericentromeric regions (Gomella et al., 2013).

Newborn Screening

Every infant born in a hospital in the United States undergoes newborn screening. Newborn screening is done before leaving the hospital, usually about day 1 or 2. Some states require follow-up at about 2 weeks. All states are required to screen for at least 34 health conditions according to the March of Dimes (MOD, n.d.). In addition to a blood test, infants undergo a hearing test and cardiovascular screening (MOD, n.d.).

GASTROINTESTINAL PROCEDURES

Barium Enema

A barium enema is used in the evaluation of the structure and function of the large intestine. The diagnosis of disorders such as Hirschsprung disease and meconium plug syndrome can easily be supported by the use of this procedure.

For the enema procedure, either air or a contrast solution (e.g., barium sulfate) is instilled and a series of films are taken under fluoroscopy. The infant must be well restrained, starting in the supine position. As the contrast solution is instilled, its flow through the bowel is observed as the infant's position is changed. A series of abdominal x-ray films should be taken once the bowel has been filled with contrast solution. Follow-up films may also be necessary to document evacuation of the contrast solution from

TABLE I.10

PLASMA ALBUMIN AND TOTAL PROTEIN IN PRETERM INFANTS FROM BIRTH TO 8 WEEKS

Gestation (Weeks)	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
Albumin g/dL																	
Reference range (95% confidence limits)	—	1.18–3.06	1.09–2.87	1.20–2.74	1.63–2.75	1.08–3.20	1.38–3.14	1.44–3.34	0.53–3.87	1.15–3.87	1.96–3.44	1.50–4.10	1.89–4.15	2.07–4.15	2.07–4.05	2.04–3.90	2.08–3.90
Corrected age																	
26–28 weeks' gestation		2.13	2.10	2.58	2.29	2.39				2.73							
29–31 weeks' gestation					2.02	2.14	2.44	2.44	2.54				2.82				
32–34 weeks' gestation								2.35	2.42	2.46	2.38	2.44				3.35	
Total Protein g/dL																	
Reference range (95% confidence limits)	—	1.28–7.94	3.03–5.03	2.18–5.84	2.64–5.80	3.26–5.66	3.63–5.81	3.57–5.87	3.57–6.59	1.52–8.62	3.85–6.91	4.69–6.95	3.32–9.16	4.17–8.25	4.26–8.08	3.73–8.47	3.24–8.76
Corrected age																	
26–28 weeks' gestation		4.07	4.45	4.84	4.49	4.45				4.41							
29–31 weeks' gestation					3.93	4.42	4.70	4.82	4.51				4.55				
32–34 weeks' gestation								4.54	4.93	4.78	4.86	4.81				4.96	

Sources: Adapted from Fanaroff, A., & Martin, R. (2002). *Neonatal-perinatal medicine: Diseases of the fetus and infant* (7th ed.). St. Louis, MO: Mosby; Reading, R. F., Ellis, R., & Fleetwood, A. (1990). Plasma albumin and total protein in preterm babies from birth to eight weeks. *Early Human Development, 22*, 81–87. doi:10.1016/0378-3782(90)90082-T

TABLE I.11

PLASMA-SERUM AMINO ACID LEVELS IN PREMATURE AND TERM NEWBORNS (μmol/L)

Amino Acid	Premature (First Day)	Newborn 16 (Before First Feeding)	16 Days to 4 Months
Taurine	105–255	101–181	
OH-proline	0–80	0	
Aspartic acid	0–20	4–12	17–21
Threonine	155–275	196–238	141–213
Serine	195–345	129–197	104–158
Asp + Glut	655–1,155	623–895	
Proline	155–305	155–305	141–245
Glutamic acid	30–100	27–77	
Glycine	185–735	274–412	178–248
Alanine	325–425	274–384	239–345
Valine	80–180	97–175	123–199
Cystine	55–75	49–75	33–51
Methionine	30–40	21–37	31–47
Isoleucine	20–60	31–47	31–47
Leucine	45–95	55–89	56–98
Tyrosine	20–220	53–85	33–75
Phenylalanine	70–110	64–92	45–65
Ornithine	70–110	66–116	37–61
Lysine	130–250	154–246	117–163
Histidine	30–70	61–93	64–92
Arginine	30–70	37–71	53–71
Tryptophan	15–45	15–45	
Citrulline	8.5–23.7	10.8–21.1	
Ethanolamine	13.4–10.5	32.7–72	
Alpha-amino-*n*-butyric acid	0–29	8.7–20.4	
Methylhistidine			

Sources: Adapted from Behrman, R. E. (1977). *Neonatal-perinatal medicine: Diseases of the fetus and infant* (2nd ed.). St. Louis, MO: Mosby; Dickinson, J. C., Rosenblum, H., & Hamilton, P. B. (1970). Ion exchange chromatography of the free amino acids in the plasma of infants under 2,500 gm at birth. *Pediatrics, 45*, 606; Klaus, M. H., & Fanaroff, A. A. (Eds.). (2001). *Care of the high-risk neonate* (5th ed.). Philadelphia, PA: WB Saunders.

TABLE I.12

URINE AMINO ACID LEVELS IN NORMAL NEWBORNS (μmol/L)

Amino Acid	μmol/day
Cysteic acid	Tr–3.32
Phosphoethanolamine	Tr–8.86
Taurine	7.59–7.72
OH-proline	0–9.81
Aspartic acid	Tr
Threonine	0.176–7.99
Serine	Tr–20.7
Glutamic acid	0–1.78
Proline	0–5.17
Glycine	0.176–65.3
Alanine	Tr–8.03
Alpha-aminoadipic acid	
Alpha-amino-*n*-butyric acid	0–0.47
Valine	0–7.76
Cystine	0–7.96
Methionine	Tr–0.892
Isoleucine	0–6.11
Tyrosine	0–1.11
Phenylalanine	0–1.66
Beta-aminoisobutyric acid	0.264–7.34
Ethanolamine	Tr–79.9
Ornithine	Tr–0.554
Lysine	0.33–9.79
1-Methylhistidine	Tr–8.64

(*continued*)

TABLE I.12

URINE AMINO ACID LEVELS IN NORMAL NEWBORNS (µmol/L) (*continued*)

Amino Acid	µmol/day
3-Methylhistidine	0.11–3.32
Carnosine	0.044–4.01
Beta-aminobutyric acid	
Cystathionine	
Homocitrulline	
Arginine	0.088–0.918
Histidine	Tr–7.04
Sarcosine	
Leucine	Tr–0.918

Sources: Adapted from Fanaroff, A. A., & Martin, R. J. (Eds.). (1997). *Neonatal-perinatal medicine: Diseases of the fetus and infant* (6th ed.). St. Louis, MO: Mosby; Klaus, M. H., & Fanaroff, A. A. (Eds.). (2001). *Care of the high-risk neonate* (5th ed.). Philadelphia, PA: WB Saunders; Meites, S. (Ed.). (1997). *Pediatric clinical chemistry: A survey of normals, methods, and instruments*. Washington, DC: American Association for Clinical Chemistry.

TABLE I.13

CEREBROSPINAL FLUID VALUES OF HEALTHY TERM NEWBORNS

	Age			
Component	**Birth to 24 Hours**	**1 Day**	**7 Days**	**Over 7 Days**
Color	Clear or xanthochromic	Clear or xanthochromic	Clear or xanthochromic	
Red blood cells (cells/mm^3)	9 (0–1,070)	23 (6–630)	3 (0–48)	
Polymorphonuclear leukocytes (cells/mm^3)	3 (0–70)	7 (0–26)	2 (0–5)	
Lymphocytes (cells/mm^3)	2 (0–20)	5 (0–16)	1 (0–4)	
Protein (mg/dL)	63 (32–240)	73 (40–148)	47 (27–65)	
Glucose (mg/dL)	51 (32–78)	48 (38–64)	55 (48–62)	
Lactate dehydrogenase (IU/L)	22–73	22–73	22–73	0–40

Sources: From Klaus, M. H., & Fanaroff, A. A. (Eds.). (2002). *Klaus & Fanaroff's neonatal-perinatal medicine: Diseases of the fetus and infant* (6th ed.). St. Louis, MO: Mosby; Naidoo, B. T. (1968, September 14). The cerebrospinal fluid in the healthy newborn infant. *South African Medical Journal, 42*(35), 933–935. Retrieved from https://journals.co.za/content/m_samj/42/35/AJA20785135_35391; Neches, W., & Platt, M. (1968). Cerebrospinal fluid LDH in 287 children, including 53 cases of meningitis of bacterial and non-baterial etiology. *Pediatrics, 41*, 1097–1103. Retrieved from https://pediatrics.aappublications.org/content/41/6/1097

TABLE I.14

CEREBROSPINAL FLUID VALUES IN VERY-LOW-BIRTH-WEIGHT INFANTS ON BASIS OF BIRTH WEIGHT

	≤1,000 g		1,001–1,500 g	
	Mean ± SD	**Range**	**Mean ± SD**	**Range**
Birth weight (g)	763 ± 115	550–980	1,278 ± 152	1,020–1,500
Gestational age (weeks)	26 ± 1.3	24–28	29 ± 1.4	27–33
Leukocytes/mm^3	4 ± 3	0–14	6 ± 9	0–44
Erythrocytes/mm^3		0–19,050	786 ± 1,879	0–9,750
PMN leukocytes (%)	6 ± 15	0–66	9 ± 17	0–60
MN leukocytes (%)	86 ± 30	34–100	85 ± 28	13–100
Glucose (mg/dL)	61 ± 34	29–217	59 ± 21	31–109
Protein (mg/dL)	150 ± 56	95–370	132 ± 3	45–227

MN, mononuclear; PMN, polymorphonuclear.

Source: Modified from Rodriquez, A. F., Kaplan, S. L., & Mason, E. O., Jr. (1990). Cerebrospinal fluid values in the very low birth weight infant. *Journal of Pediatrics, 116*, 971–974. doi:10.1016/S0022-3476(05)80663-8

TABLE I.15

CEREBROSPINAL FLUID VALUES IN VERY-LOW-BIRTH-WEIGHT INFANTS (1,001–1,500 G) BY CHRONOLOGIC AGE

	Postnatal Age (Days)					
	0–7		**8–28**		**29–84**	
Component	**Mean ± SD**	**Range**	**Mean ± SD**	**Range**	**Mean ± SD**	**Range**
Birth weight (g)	1,428 ± 107	1,180–1,500	1,245 ± 162	1,020–1,480	1,211 ± 86	1,080–1,300
Gestational age at birth (weeks)	31 ± 1.5	28–33	29 ± 1.2	27–31	29 ± 0.7	27–29
Leukocytes/mm^3	4 ± 4	1–10	7 ± 11	0–44	8 ± 8	0–23
Erythrocytes/mm^3	407 ± 853	0–2,450	1,101 ± 2,643	0–9,750	661 ± 1,198	0–3,800
PMN (%)	4 ± 10	0–28	10 ± 19	0–60	11 ± 19	0–48
Glucose (mg/dL)	74 ± 19	50–96	59 ± 23	39–109	47 ± 13	31–76
Protein (mg/dL)	136 ± 35	85–176	137 ± 46	54–227	122 ± 47	45–187

Source: Modified from Rodriquez, A. F., Kaplan, S. L., & Mason, E. O., Jr. (1990). Cerebrospinal fluid values in the very low birth weight infant. *Journal of Pediatrics, 116*, 971–974. doi:10.1016/S0022-3476(05)80663-8

TABLE I.16

THYROID FUNCTION IN FULL-TERM AND PRETERM INFANTS

	Serum T_4 Concentration in Premature and Term Infants					Serum-Free T_4 Index in Premature and Term Infants				
	Estimated Gestational Age (Weeks)									
	30–31	32–33	34–35	36–37	Term	30–31	32–33	34–35	36–37	Term
Cord										
Mean	6.5[a]	7.5[b]	6.7[b]	7.5	8.2			5.6	5.6	5.9
SD	1	2.1	1.2	2.8	1.8			1.3	2	1.1
N	3	8	18	17	17			12	10	14
12–72 Hours Old										
Mean	11.5[b]	12.3[b]	12.4[b]	15.5[c]	19	13.1[d]	12.9[d]	15.5[d]	17.1	19.7
SD	2.1	3.2	3.1	2.6	2.1	2.4	2.7	3	3.5	3.5
N	12	18	17	15	6	12	14	14	14	6
3–10 Days Old										
Mean	7.7[b]	8.5[b]	10[b]	12.7[c]	15.9	8.3[d]	9[d]	12[e]	15.1	16.2
SD	1.8	1.9	2.4	2.5	3	1.9	1.8	2.3	0.7	3.2
N	7	8	9	9	29	6	9	5	4	11
11–20 Days Old										
Mean	7.5[c]	8.3[b]	10.5	11.2	12.2	8[f]	9.1[e]	11.8	11.3	12.1
SD	1.8	1.6	1.8	2.9	2	1.6	1.9	2.7	1.9	2
N	5	11	9	9	8	5	8	8	5	8
21–45 Days Old										
Mean	7.8[b]	8[b]	9.3[b]	11.4	12.1	8.4[f]	9[e]	10.9		11.1
SD	1.5	1.7	1.3	4.2	1.5	1.4	1.6	2.8		1.4
N	11	17	13	5	5	11	17	5		5
46–90 Days Old			30–73				34–35			
Mean		9.6		10.2	9.4					9.7
SD		1.7		1.9	1.4					1.5
N		16		17	13					10

For comparison of premature and term infants (*t* test); [a] $p < .05$; [b] $p < .001$; [c] $p < .005$; [d] $p = .001$; [e] $p = .01$; [f] $p = .005$.

Source: Adapted from Cuestas, R. A. (1978, June). Thyroid function in healthy premature infants. *Journal of Pediatrics, 92*(6), 963–967. doi:10.1016/S0022-3476(78)80378-3

the bowel. Evaluation of the bowel is essential after this procedure to prevent constipation or obstruction. Assessment of bowel elimination is an important nursing concern after barium enema.

Upper Gastrointestinal Series With Small Bowel Follow-Through

As with the barium enema, barium sulfate or some other water-soluble contrast solution is used for the upper GI series with small bowel follow-through. However, the contrast solution is swallowed so that the upper GI tract can be examined. The three main areas examined are (1) the esophagus (for size, patency, reflux, and presence of a fistula or swallowing abnormality), (2) the stomach (for anatomic abnormalities, patency, and motility), and (3) the small intestine (for strictures, patency, and function).

Follow-up x-ray films may be desirable to evaluate both the emptying ability of the stomach and intestinal motility as the contrast material moves through the small bowel. Again, care of the infant includes assessment of temperature and cardiac and respiratory status throughout the procedure. The nurse should be alert for reflux or vomiting, which can be accompanied by aspiration. Evacuation of contrast material from the bowel remains a concern after upper GI series with small bowel follow-through and should be monitored by the nurse. It is also possible for fluid to be pulled out of the vascular compartment and into the bowel, resulting in hypotension. It is imperative that the healthcare team assess the infant for signs of these complications.

Rectal Suction Biopsy

Rectal biopsy is a procedure commonly used to help determine the presence or absence of ganglion cells in the bowel (the latter condition is seen in Hirschsprung disease). Before a rectal biopsy, it is essential to obtain bleeding times, prothrombin time, partial thromboplastin time, and platelet counts, as well as a spun hematocrit, to ensure that the infant is in no danger of excessive bleeding.

The infant is positioned supine with the legs held toward the abdomen. Small specimens of rectal tissue from the mucosal and submucosal levels are excised with a suction blade apparatus inserted through the anus into the bowel. The section of the pathology department that deals with the composition of ganglion cells evaluates the specimens.

Care of the infant after rectal suction biopsy should focus on assessments for bleeding or intestinal perforation. These assessments should include evaluation of vital signs for increased heart rate or decreased blood pressure, fever, persistent guaiac-positive stools, or frank rectal bleeding.

Liver Biopsy

Open or closed liver biopsy may be required for neonates. Open liver biopsy is a surgical procedure that requires general anesthesia, whereas a closed liver biopsy may be done using local anesthesia. As with the rectal biopsy, coagulation studies are essential, including bleeding time, platelet count, and spun hematocrit. Preoperative care may include sedation of the infant, requiring frequent monitoring of vital signs. Throughout the procedure, assessment of vital signs is essential for identifying changes in hemodynamics or respiratory status. After the procedure, assessment of vital signs for signs and symptoms of hemorrhage is essential. Indications of hemorrhage include decreases in the hemoglobin and hematocrit, which makes laboratory monitoring an important element of post biopsy care. The biopsy site must be evaluated for signs of active bleeding, ecchymosis, swelling, or infection.

GENITOURINARY PROCEDURES

Cystoscopy

Cystoscopy permits direct visualization of the urinary structures, including the bladder, urethra, and urethral orifices, allowing diagnosis of abnormalities in the structure of the bladder and urinary tract.

Cystoscopy is performed using general anesthesia. Preparation of the urethral opening with an antiseptic solution is followed by sterile draping. The lubricated cystoscope is inserted through the urethra, and the urinary structures are examined.

As with any patient who has had anesthesia, postprocedural care includes vital sign assessment. However, particular attention should be paid to assessing for adequate urinary output, the presence of hematuria, and signs of infection (Pagana & Pagana, 2013).

Excretory Urography and Intravenous Pyelography

Excretory urography and intravenous pyelography complement cystoscopic evaluation because they allow the examiner not only to evaluate structures but also to focus on the function of those structures. Small amounts of contrast media are injected by the intravenous route, and as the contrast material is excreted through the urinary system, a sequence of x-ray films is taken. The configuration of organs and the rate of excretion of the contrast media are reflected in these films.

Excretory urography and intravenous pyelography are relatively safe for use in neonates and should cause no postprocedural complications.

Voiding Cystourethrogram

The purpose of a voiding cystourethrogram is to visualize the lower urinary tract after instillation of contrast media through urethral catheterization. The infant's bladder is emptied after catheterization and then filled with the contrast media. Serial films under fluoroscopy in a variety of positions are taken during voiding. After voiding, additional films are obtained. Pathologic results of a voiding cystourethrogram demonstrate residual urine in the bladder, such as with a neurogenic bladder, posterior valve obstructions, or vesicoureteral reflux.

As with cystoscopy, the infant should be evaluated for hematuria; the baby should also be checked for signs of infection (fever, cloudy or sedimented urine, foul-smelling urine) in the event of contaminated catheterization.

Electroencephalography

An electroencephalographic examination records the electrical activity of the brain. Numerous electrodes are placed at precise locations on the infant's head to record electrical impulses from various parts of the brain. This procedure can be important for diagnosing lesions or tumors, for identifying nonfunctional areas of the brain, or for pinpointing the focus of seizure activity.

The infant may require sedation during this procedure to prevent crying or movement. As much equipment as is safely possible should be removed to reduce electrical interference. Also, calming procedures, such as reducing light stimulation or warming the environment, may help quiet the infant during electroencephalography. The infant should be closely observed throughout the procedure for any signs of seizure activity.

RESPIRATORY PROCEDURES

Pulse Oximetry

Pulse oximetry is a widely used, noninvasive method of monitoring arterial blood oxygenation saturations (Sao_2). The Sao_2 is the ratio of oxygenated hemoglobin to total hemoglobin. A single probe, attached to an infant's extremity or digit, uses light emitted at different wavelengths, which is absorbed differently by saturated and unsaturated hemoglobin. The change in the light during arterial pulses is used to calculate the oxygen saturation. Pulse oximetry saturations reflect a more accurate measure of actual hemoglobin saturation. Saturations obtained by blood gas sample are calculated using a hemoglobin of 15% (Goetzman & Wennberg, 1999).

Proper placement of the probe should be assessed regularly because movement, environmental light, edema, and diminished perfusion can reduce the accuracy of readings. The probe should be rotated every few hours to prevent skin breakdown at the site.

End-Tidal Carbon Dioxide Monitoring

End-tidal carbon dioxide (CO_2) monitoring is used routinely in pediatrics and in adult ICUs. Its use in neonates, especially the smaller baby, is not yet practical as a continuing therapy because the adapters are heavy and create excess dead space in the ventilator system. End-tidal CO_2 monitoring is most useful during intubation procedures for determining if endotracheal intubation rather than esophageal intubation has occurred (Goetzman & Wennberg, 1999; Yorgin & Rhee, 1998).

Bronchoscopy

Bronchoscopy of the newborn is performed to visualize the upper and lower airways and to collect diagnostic specimens. The procedure can be done in the NICU using a flexible bronchoscope, or it can be performed under general anesthesia in the operating room using either a flexible or rigid bronchoscope. The flexible bronchoscope is preferable for examining the lower airways of an intubated patient or for examining a patient with mandibular hypoplasia. A rigid bronchoscope is more advantageous in situations requiring removal of foreign bodies and for evaluation of patients with H-type tracheoesophageal fistula, laryngotracheoesophageal clefts, and bilateral abductor paralysis of the vocal cords (Wood, 1998). Examination of structures by direct visualization provides the opportunity to identify congenital anomalies, obstructions, masses, or mucous plugs and to evaluate stridor or respiratory dysfunction.

Bronchoscopy done at the bedside requires the nurse to assist with positioning, sedation, and monitoring of vital signs. Whether the infant undergoes flexible or rigid bronchoscopy, respiratory and cardiovascular monitoring should be continued in the immediate postprocedural period. Possible complications related to these procedures include bronchospasm, laryngeal spasms, laryngeal edema, or pneumothorax or bradycardia resulting in hypoxia.

SUMMARY

Marked technical advances over the past two decades have produced a variety of imaging methods for the diagnosis, treatment, and evaluation of neonates. Sizable expenditures have been directed toward improving image presentation and quality on the assumption that a trained clinical eye can make diagnostic use of the data provided. Investigations are useful only insofar as they reduce the diagnostic uncertainty. The final product of any radiologic imaging procedure is not a set of photographic pictures, but a diagnostic opinion that should be beneficial to the infant's management. Before initiating any imaging method, physicians should consider whether further information is really needed, and they should select the imaging technique that will give the required information with sufficient reliability and with minimal risk to the patient. The value of any diagnostic imaging examination must be balanced against the potential hazards. In addition to care of the newborn during and after a procedure, nursing care of newborns and infants undergoing diagnostic procedures requires a knowledge of the expected outcomes and methods so that the best result possible is obtained. Nurses must also be knowledgeable about normal values for the laboratory tests commonly used in the care of newborns and infants.

REFERENCES

Alpen, E. L. (1998). *Radiation biophysics* (2nd ed.). San Diego, CA: Academic Press.

Bajaj, K., & Gross, S. (2015). Genetic aspects of perinatal disease and prenatal diagnosis. In R. Martin, A. Fanaroff, & M. Walsh (Eds.), *Fanaroff & Martin's neonatal-perinatal medicine: Diseases of the fetus and infant* (10th ed., chapter 11). St. Louis, MO: Elsevier Mosby.

Bansal, M. (2015). Cardiovascular problems of the neonate. In R. Martin, A. Fanaroff, & M. Walsh (Eds.), *Fanaroff & Martin's neonatal-perinatal medicine: Diseases of the fetus and infant* (9th ed., chapter 85). St. Louis, MO: Elsevier Mosby.

Behrman, R. E. (1977). *Neonatal-perinatal medicine: Diseases of the fetus and infant* (2nd ed.). St. Louis, MO: Mosby.

Bellenger, N. G., Burgess, M. I., Ray, S. G., Lahiri, A., Coats, A. J., Cleland, J. G., & Pennell, D. J. (2000). Comparison of left ventricular ejection fraction and volumes in heart failure by echocardiography, radionuclide ventriculography and cardiovascular magnetic resonance; are they interchangeable? *European Heart Journal, 21*(16), 1387–1396. doi:10.1053/euhj.2000.2011

Bushong, S. C. (1999). *Diagnostic ultrasound: Essentials of medical imaging series*. New York, NY: McGraw-Hill.

Bushong, S. C. (2000). *Computed tomography: Essentials of medical imaging series*. New York, NY: McGraw-Hill.

Bushong, S. C. (2001). *Radiologic science for technologists physics, biology, and protection* (7th ed.). St. Louis, MO: Mosby.

Bushong, S. C. (2003). *Magnetic resonance imaging: Physical and biological principles* (3rd ed.). St. Louis, MO: Mosby.

Bushong, S. C. (2013). *Radiologic science for technologists: Physics, biology, and protection* (10th ed.). St. Louis, MO: Elsevier Mosby.

Cooke, R., Hollis, B., Conner, C., Watson, D., Werkman, S., & Chesney, R. (1990). Vitamin D and mineral metabolism in the very low birth weight infant receiving 400 IU of vitamin D. *Journal of Pediatrics, 116*(3), 423–428. doi:10.1016/s0022-3476(05)82837-9

Cornblath, M., & Schwartz, R. (Eds.). (1976). *Disorders of carbohydrate metabolism* (2nd ed.). Philadelphia, PA: WB Saunders.

Cuestas, R. A. (1978, June). Thyroid function in healthy premature infants. *Journal of Pediatrics, 92*(6), 963–967. doi:10.1016/S0022-3476(78)80378-3

Dickinson, J. C., Rosenblum, H., & Hamilton, P. B. (1970). Ion exchange chromatography of the free amino acids in the plasma of infants under 2,500 gm at birth. *Pediatrics, 45*, 606. Retrieved from https://pediatrics.aappublications.org/content/45/4/606

Dort, J. C., Sadler, D., Hu, W., Wallace, C., La Forge, P., & Sevick, R. (2001). Screening for cerebellopontine angle tumours: Conventional MRI vs T2 fast spin echo MRI. *Canadian Journal Neurological Sciences, 28*(1), 47–50. doi:10.1017/S0317167100052549

Dowd, S. B., & Tilson, E. R. (1999). *Practical radiation protection and applied radiobiology* (2nd ed.). Philadelphia, PA: Saunders.

Drummond, L. M. (1979). Creatine phosphokinase levels in the newborn and their use in screening for Duchenne muscular dystrophy. *Archives of Disease in Childhood, 54*, 362–366. doi:10.1136/adc.54.5.362

Erenberg, F. (2011). Fetal cardiac physiology and fetal cardiovascular assessment. In R. Martin, A. Fanaroff, & M. Walsh (Eds.), *Fanaroff & Martin's neonatal-perinatal medicine* (9th ed., chapter 82). St. Louis, MO: Elsevier Mosby.

Fanaroff, A. A., & Martin, R. J. (Eds.). (1987). *Neonatal-perinatal medicine: Diseases of the fetus and infant* (4th ed.). St. Louis, MO: Mosby.

Fanaroff, A. A., & Martin, R. J. (Eds.). (1997). *Neonatal-perinatal medicine: Diseases of the fetus and infant* (6th ed.). St. Louis, MO: Mosby.

Fanaroff, A. A., & Martin, R. J. (Eds.). (2002). *Neonatal-perinatal medicine: Diseases of the fetus and infant* (7th ed.). St. Louis, MO: Mosby.

Flanagan, M. F., Yeager, S. B., & Weindling, S. N. (2015). Cardiac disease. In M. G. MacDonald & M. M. K. Seshia (Eds.), *Avery's neonatology pathophysiology & management of the newborn* (7th ed., pp. 487–547). Philadelphia, PA: Lippincott Williams & Wilkins.

Fogel, M. A., Rychik, J., Chin, A. J., Hubbard, A., & Weinberg, P. M. (2001). Evaluation and follow-up of patients with left ventricular apical to aortic conduits with 2D and 3D magnetic resonance imaging and Doppler echocardiography: A new look at an old operation. *American Heart Journal, 141*(4), 630–636. doi:10.1067/mhj.2001.113576

Glass, E. J., Hume, R., Hendry, G. M., Strange, R. C., & Forfar, J. O. (1982). Plasma alkaline phosphatase activity in rickets of prematurity. *Archives of Disease in Childhood, 57*, 373–376. doi:10.1136/adc.57.5.373

Goetzman, B. W., & Wennberg, R. P. (1999). *Neonatal intensive care handbook* (3rd ed.). St. Louis, MO: Mosby.

Gomella, T. L., Cunningham, M. D., & Eyal, F. G. (2013). *Neonatology: Management, procedures, on-call problems, diseases, and drugs* (7th ed.). New York, NY: McGraw-Hill.

Hamilton, B. A., & Wynshaw-Boris, A. (2009). Basic genetics and patterns of inheritance. In R. K. Creasy, R. Resnik, J. D. Iam, C. J. Lockwood, & T. Moore (Eds.), *Creasy and Resnik's maternal-fetal medicine: Principles and practice* (6th ed., pp. 3–36). Philadelphia, PA: Saunders Elsevier.

Heck, L. J., & Erenberg, A. (1987, January). Serum glucose levels in term neonates during the first 48 hours of life. *Pediatric Research, 110*(1), 119–122.

Hilton, S., & Edwards, D. K., III. (2006). *Practical pediatric radiology* (3rd ed.). Philadelphia, PA: Saunders Elsevier.

Huda, W., Chamberlain, C. C., Rosenbaum, A. E., & Garrisi, W. (2001). Radiation doses to infants and adults undergoing head CT examinations. *Medical Physics, 28*(3), 393–399. doi:10.1118/1.1350435

Huppi, P. S., Murphy, B., Maier, S. E., Zientara, G. P., Inder, T. E., Barnes, P. D., & Volpe, J. J. (2001). Microstructural brain development after perinatal cerebral white matter injury assessed by diffusion tensor magnetic resonance imaging. *Pediatrics, 107*(3), 455–460. doi:10.1542/peds.107.3.455

Ichikawa, I. (Ed.). (1990). *Pediatric textbook of fluids and electrolytes*. Baltimore, MD: Lippincott Williams & Wilkins.

Juhl, J. H., Crummy, A. B., & Kuhlman, J. E. (1998). *Paul and Juhl's essentials of radiologic imaging* (7th ed.). Philadelphia, PA: Lippincott Williams & Wilkins.

Klaus, M. H., & Fanaroff, A. A. (Eds.). (2001). *Care of the high-risk neonate* (5th ed.). Philadelphia, PA: WB Saunders.

Klaus, M. H., & Fanaroff, A. A. (Eds.). (2002). *Klaus & Fanaroff's neonatal-perinatal medicine: Diseases of the fetus and infant* (6th ed.). St. Louis, MO: Mosby.

Krishnamoorthy, K. S., Soman, T. B., Takeoka, M., & Schaefer, P. W. (2000). Diffusion-weighted imaging in neonatal cerebral infarction: Clinical utility and follow-up. *Journal of Child Neurology, 15*(9), 592–602. doi:10.1177/088307380001500905

Kuller, J. A., & Cefalo, R. C. (1996). *Prenatal diagnosis and reproductive genetics*. St. Louis, MO: Mosby.

Lansberg, M. G., O'Brien, M. W., Tong, D. C., Moseley, M. E., & Albers, G. W. (2001). Evolution of cerebral infarct volume assessed by diffusion-weighted magnetic resonance imaging. *Archives of Neurology, 58*(4), 613–617. doi:10.1001/archneur.58.4.613

Lewis, P. J., Siegel, A., Siegel, A. M., Studholme, C., Sojkova, J., Roberts, D. W., . . . Williamson, P. D. (2000). Does performing image registration and subtraction in ictal brain SPECT help localize neocortical seizures? *Journal of Nuclear Medicine, 41*(10), 1619–1626. Retrieved from http://jnm.snmjournals.org/content/41/10/1619.full.pdf+html

Lichtenstein, P., Specker, B. L., Tsang, R. C., Mimouni, F., & Gormley, C. (1986). Calcium-regulating hormones and minerals from birth to 18 months of age: A cross-sectional study. I. Effects of sex, race, age, season, and diet on vitamin D status. *Pediatrics, 77*, 883–890. Retrieved from https://pediatrics.aappublications.org/content/77/6/883

Liebman, J., & Plonsey, R. (1977). Electrocardiography. In A. J. Moss, F. H. Adams, & G. C. Emmanouilides (Eds.), *Heart disease in infants, children and adolescents* (2nd ed.). Baltimore, MD: Lippincott Williams & Wilkins.

Lin, J. W., Laine, A. F., & Bergmann, S. R. (2001). Improving pet-based physiological quantification through methods of wavelet denoising. *IEEE Transactions on Biomedical Engineering, 48*(2), 202–212. doi:10.1109/10.909641

March of Dimes. (n.d.). Newborn screening tests for your baby. Retrieved from https://www.marchofdimes.org/baby/newborn-screening-tests-for-your-baby.aspx

Martin, R. J., Fanaroff, A. A., & Walsh, M. C. (2015). *Fanaroff & Martin's neonatal-perinatal medicine: Diseases of the fetus and infant* (10th ed.). Philadelphia, PA: Elsevier/Saunders.

McLean, S. D. (2015). Congenital anomalies. In M. G. MacDonald & M. K. Seshia (Eds.), *Avery's neonatology pathophysiology & management of the newborn* (7th ed., pp. 683–698). Philadelphia, PA: Lippincott Williams & Wilkins.

Meites, S. (1975, January). Normal total plasma calcium in the newborn. *Critical Reviews of Clinical Laboratory Sciences, 6*(1), 1–18. doi:10.3109/10408367509151562

Meites, S. (Ed.). (1997). *Pediatric clinical chemistry: A survey of normals, methods, and instruments*. Washington, DC: American Association for Clinical Chemistry.

Naidoo, B. T. (1968, September 14). The cerebrospinal fluid in the healthy newborn infant. *South African Medical Journal, 42*(35), 933–935. Retrieved from https://journals.co.za/content/m_samj/42/35/AJA20785135_35391

National Committee for Clinical Laboratory Standards. (1994). *Sweat testing: Sample collection and quantitative analysis: Approved guideline*. Wayne, PA: Author.

National Council on Radiation Protection and Measurements. (1993a). *A practical guide to the determination of human exposure to radiofrequency fields* (NCRP Report No. 119). Bethesda, MD: Author.

National Council on Radiation Protection and Measurements. (1993b). *Research needs for radiation protection* (NCRP Report No. 117). Bethesda, MD: Author.

National Council on Radiation Protection and Measurements. (1993c). *Risk estimates for radiation protection* (NCRP Report No. 15). Bethesda, MD: Author.

National Council on Radiation Protection and Measurements. (2018). *Statements 1, 3, and 4*. Retrieved from https://ncrponline.org/publications/statements

Neches, W., & Platt, M. (1968). Cerebrospinal fluid LDH in 287 children, including 53 cases of meningitis of bacterial and non-baterial etiology. *Pediatrics, 41*, 1097–1103. Retrieved from https://pediatrics.aappublications.org/content/41/6/1097

Nelson, N., Finnstrom, O., & Larsson, L. (1987). Neonatal reference values for ionized calcium, phosphate and magnesium. Selection of reference population by optimality criteria. *Scandinavian Journal of Clinical Laboratory Investigations, 47*(2), 111–117. doi:10.3109/00365518709168878

Nolte, U. G., Finsterbusch, J., & Frahm, J. (2000). Rapid isotropic diffusion mapping without susceptibility artifacts: Whole brain studies using diffusion-weighted single-shot steam MR imaging. *Magnetic Resonance in Medicine, 44*(5), 731–736. doi:10.1002/1522-2594(200011)44:5<731::AID-MRM11>3.0.CO;2-1

Pagana, K. D., & Pagana, T. J. (2013). *Mosby's diagnostic and laboratory test reference* (11th ed.). St. Louis, MO: Elsevier Mosby.

Peled, S., & Yeshurun, Y. (2001). Super Resolution in MRI: Application to human white matter fiber tract visualization by diffusion tensor imaging. *Magnetic Resonance in Medicine, 45*(1), 29–35. doi:10.1002/1522-2594(200101)45:1<29::AID-MRM1005>3.0.CO;2-Z

Peterson, B. S., Vohr, B., Staib, L. H., Cannistraci, C. J., Dolberg, A., Schneider, K. C., . . . Ment, L. R. (2000). Regional brain volume abnormalities and long-term cognitive outcome in preterm infants. *Journal of the American Medical Association, 284*(15), 1939–1947. doi:10.1001/jama.284.15.1939

Reading, R. F., Ellis, R., & Fleetwood, A. (1990). Plasma albumin and total protein in preterm babies from birth to eight weeks. *Early Human Development, 22*, 81–87. doi:10.1016/0378-3782(90)90082-T

Rodriquez, A. F., Kaplan, S. L., & Mason, E. O., Jr. (1990). Cerebrospinal fluid values in the very low birth weight infant. *Journal of Pediatrics, 116*, 971–974. doi:10.1016/S0022-3476(05)80663-8

Rushe, T. M., Rifkin, L., Stewart, A. L., Townsend, J. P., Roth, S. C., Wyatt, J. S., & Murray, R. M. (2001). Neuropsychological outcome at adolescence of very preterm birth and its relation to brain structure. *Developmental Medicine and Child Neurology, 43*(4), 226–233. doi:10.1017/S0012162201000433

Schaffer, A. J. (1971). *Diseases of the newborn* (3rd ed.). Philadelphia, PA: WB Saunders.

Schierlitz, L., Dumanli, H., Robinson, J. N., Burrows, P. E., Schreyer, A. G., Kikinis, R., . . . Tempany, C. M. (2001). Three-dimensional magnetic resonance imaging of fetal brains. *Lancet, 357*(9263), 1177–1178. doi:10.1016/S0140-6736(00)04375-0

Shenai, J. P., Chytil, F., Jhaveri, A., & Stahlman, M. T. (1981, August). Plasma vitamin A and retinol-binding protein in premature and term neonates. *Journal of Pediatrics, 99*(2), 302–305. doi:10.1016/S0022-3476(81)80484-2

Sie, L. T., Barkhof, F., Lafeber, H. N., Valk, J., & van der Knaap, M. S. (2000). Value of fluid-attenuated inversion recovery sequences in early MRI of the brain in neonates with a perinatal hypoxic-ischemic encephalopathy. *European Radiology, 10*(10), 1594–1601. doi:10.1007/s003300000482

Sinson, G., Bagley, L. J., Cecil, K. M., Torchia, M., McGowan, J. C., Lenkinski, R. E., . . . Grossman, R. I. (2001). Magnetization transfer imaging and proton MR spectroscopy in the evaluation of axonal injury: Correlation with clinical outcome after traumatic brain injury. *American Journal of Neuroradiology, 22*(1), 143–151. Retrieved from http://www.ajnr.org/content/22/1/143

Statlan, B. E., et al. (1978). *Clinical Chemistry, 24*, 1010.

Swischuk, L. E. (1995). *Differential diagnosis in pediatric radiology*. Baltimore, MD: Lippincott Williams & Wilkins.

Swischuk, L. E. (2003). *Imaging of the newborn, infant, and young child* (5th ed.). Baltimore, MD: Lippincott Williams & Wilkins.

Tierney, M. C., Varga, M., Hosey, L., Grafman, J., & Braun, A. (2001). PET evaluation of bilingual language compensation following early childhood brain damage. *Neuropsychologia, 39*(2), 114–121. doi:10.1016/S0028-3932(00)00106-8

Tietz, N. W. (Ed.). (1988). *Textbook of clinical chemistry*. Philadelphia, PA: WB Saunders.

Treves, S. T. (1995). *Pediatric nuclear medicine* (2nd ed.). New York, NY: Springer.

Verklan, M., & Walden, M. (2014). *Core curriculum for neonatal intensive care nursing* (5th ed.). St. Louis, MO: Elsevier Mosby.

Wallach, J. B. (1983). *Interpretation of pediatric tests*. Boston, MA: Little, Brown.

Weissleder, R., & Mahmood, U. (2001). Molecular imaging. *Radiology, 219*(2), 316–333. doi:10.1148/radiology.219.2.r01ma19316

Wilford, B. S., & Taussig, L. M. (1998). Cystic fibrosis: General overview. In L. M. Taussig & L. I. Landau (Eds.), *Pediatric respiratory medicine*. St. Louis, MO: Mosby.

Wood, R. E. (1998). Diagnostic and therapeutic procedures in pediatric pulmonary patients. In L. M. Taussig & L. I. Landau (Eds.), *Pediatric respiratory medicine*. St. Louis, MO: Mosby.

Yorgin, P. D., & Rhee, K. H. (1998). Gas exchange and acid-base physiology. In L. M. Taussig & L. I. Landau (Eds.), *Pediatric respiratory medicine*. St. Louis, MO: Mosby.

Guidelines for Supporting Skin-to-Skin Contact in the NICU

Raylene M. Phillips

11

INTRODUCTION

Continuous skin-to-skin contact (SSC) with the mother is the normal environment and developmental expectation for all newborns (Bergman, 2014). The first few days after birth are a critical period for many physiologic and neurologic processes that occur during the complex and multifaceted adaptation to post-uterine life for both the baby and the mother. Some of these neurological processes occur only during the first day after birth, and if they are not allowed to occur, the window of opportunity is missed (Bartocci et al., 2000). Continuous SSC with the mother is how physiologic and hormonal regulation is designed to occur for the newborn and very young infant, as documented in both animal and human studies (Chi Luong, Long Nguyen, Huynh Thi, Carrara, & Bergman, 2016; Gallagher, 1992; Hofer, 1994).

Most term and preterm babies are more stable in SSC with the mother after birth than in any other location (Bergman, Linley, & Fawcus, 2004; Chi Luong et al., 2016). The mother's body is designed to be the regulator of the baby's physiologic stability and has been shown to do so even for babies born prematurely (Bergman et al., 2004; Chi Luong et al., 2016; Feldman, Rosenthal, & Eidelman, 2014; Hofer, 1994; Parmar et al., 2009). Separation, or the absence of contact with the mother's or a primary caregiver's body, induces stress, dysregulation, and even neurologic changes in infant mammals (Arabadzisz et al., 2010; Loman & Gunnar, 2010; Michelsson, Christensson, Rothganger, & Winberg, 1996; Morgan, 2013; Reite, Seiler, & Short, 1978; Sabatini et al., 2007; Shonkoff et al., 2012). This stress is accompanied by high levels of cortisol, which, if prolonged, leads to toxic stress, defined by Shonkoff as "stress in the absence of the buffering protection of adult support" (Shonkoff, 2010, p. 360). Due to the stress and dysregulation that results whenever babies are apart from the mother or another primary caregiver, Dr. Nils Bergman strongly advocates for a policy of zero separation except in the case of life-threatening emergencies, surgical procedures, or severe medical instability (Bergman, 2014, 2015). The need for SSC to support physiologic stability and neuroprotection is inversely proportional to gestational age. Babies born prematurely require SSC to maintain stability and continue gestational maturation. The process of mother–infant bonding and attachment is intricately linked to SSC (Hofer, 2006). If the mother is unavailable, the father or another primary caregiver can prevent toxic stress and provide many of the benefits of SSC. Although continuous SSC is necessary for optimal normal development, even intermittent SSC provides well-documented short- and long-term benefits for babies and parents (Conde-Agudelo & Diaz-Rossello, 2014; Kirsten, Bergman, & Hann, 2001; Mooncey, Giannakoulopoulos, Glover, Acolet, & Modi, 1997; Welch et al., 2014).

Monitoring, nursing, and medical care, as well as many procedures, can be done during SSC. Babies can receive the same excellent medical and nursing care on the mother's body rather than in an incubator, on a bed, or on another surface (Bergman, 2015; Nyqvist et al., 2010). It is well documented that SSC reduces signs of pain during painful procedures (Gray, Miller, Philipp, & Blass, 2002; Johnston et al., 2003). Skin-to-skin contact can be done safely during transport from place to place within the hospital and even from hospital to hospital, and the baby will be more physiologically stable while in SSC (Sontheimer, Fischer, & Buch, 2004). If the mother is not available, the father or another primary caregiver can provide SSC during transport.

If the baby shows signs of instability during SSC, an assessment should be done during SSC and adjustments made as needed. Staff must be able to recognize preterm behavioral signs of stress and dysregulation and know how to respond appropriately. Parents should also be taught how to recognize their baby's signs of stress and how to respond (Als, 1984). SSC should only be discontinued if instability does not resolve after appropriate adjustments are made.

Parents should have round-the-clock access to their baby without limitations or restrictions. Parents need facilities to support their presence for continuous or prolonged SSC and for participation in their baby's care, including a place to sleep, access to food and drink, and whatever is needed for activities of daily living while their baby is in the NICU (Craig et al., 2015; Hall, Phillips, & Hynan, 2016; Nyqvist & Engvall, 2009; Sanders & Hall, 2018).

SSC supports early and exclusive breastfeeding (Bramson et al., 2010; Mikiel-Kostyra, Mazur, & Boltruszko, 2002; Nyqvist, 2008; Uvnas-Moberg, 2003). Mothers need support to initiate milk expression in the first hour and ongoing support to maintain an adequate milk supply. Even very premature babies are able to suckle when in continuous SSC with mother and may begin suckling as early as after a 29-week gestation period. As they mature, suckling becomes breastfeeding. SSC supports early discharge due to

increased stability and earlier full feedings (Nyqvist et al., 2010). Appropriate follow-up is essential (Penalva & Schwartzman, 2006).

It is vitally important that NICU staff from all disciplines actively and consistently promote SSC and encourage parental involvement in their baby's care. NICU staff must be given the education and training to effectively help parents understand how important they are to their baby's short- and long-term well-being (Chia, Sellick, & Gan, 2006; Ludington-Hoe, Morgan, & Abouelfettoh, 2008; Wallin, Rudberg, & Gunningberg, 2005). Parents should be offered adequate support for physical, psychological, and mental well-being and should have access to psychosocial support from a psychologist or other mental health professionals if needed or desired (Craig et al., 2015; Hall et al., 2016; Nyqvist et al., 2010; Nyqvist & Engvall, 2009; Sanders & Hall, 2018).

PREREQUISITES

There are no gestational limits to SSC. The only prerequisite is that the baby's skin be intact enough for handling without damage. If the baby is not receiving continuous SSC, parents should be available for a minimum of 60 minutes of SSC to support the neurologic process occurring during an entire 60-minute sleep cycle (Ludington-Hoe et al., 2008). Prolonged sessions of SSC should be encouraged. If only intermittent SSC is occurring, parents may want to practice the transfer from the bed to the parent's chest with a doll before the first SSC session. Staff should be trained and comfortable with transferring small babies from the incubator to the parent's chest. For optimal safety, if the baby is not intubated and has no arterial line, at least one extra staff is needed to help with the baby's lines and tubes. If the baby is intubated and has an arterial line, ideally two extra staff are needed to help support the initiation of SSC.

CONTRAINDICATION

Contraindications to SSC are few. Babies with extremely immature, gelatinous skin should have minimal handling until the skin matures but will benefit from the parent's presence, smell, and voice. Babies with unhealed chest or abdominal surgical wounds will also benefit from the parent's presence, smell, and voice, as well as containment with the parent's hands. If a baby has an arterial line that is not well secured, SSC should be deferred until the line can be safely secured. When babies have significant physiologic instability and cannot tolerate the movement necessary for transfer from the bed to the parent's chest, they will benefit from the parent's presence, smell, and voice, and will often have a positive response to gentle, whole-hand, containing touch. Since there is an energy cost when transferring a very preterm infant from the bed to the parent's chest, if parents are available for less than 60 minutes, they should be encouraged to support their baby with their presence, smell, voice, and gentle containing touch.

INITIATION

Whenever possible, the newly born baby should be placed immediately on the mother's abdomen or chest where assessment, stabilization, and monitoring can be performed. Plastic wrap and/or a warmed blanket should be used to enhance warmth. Continuous positive airway pressure (CPAP) can be started, and monitoring leads placed while the baby is in SSC with the mother. If more extensive resuscitation must be done on a warming table, the baby should be returned to SSC with the mother as soon as possible. If the mother is unstable, the baby can be stabilized in SSC with the father or another primary caregiver. It is important to remember that the mother's body is designed to regulate newborn infants and being in SSC, ideally with the mother, is how newborns will stabilize in the most optimal manner. If SSC has not occurred in the delivery room, it should be done as soon as possible in the NICU if no contraindications are present.

During transfer from the delivery room to another location in the hospital, the baby should remain in SSC with the mother, father, or another primary caregiver using a gurney or wheelchair. Babies on mechanical ventilation can be transferred in SSC, as they will be more stable if they are in SSC with the mother, father, or another primary caregiver. The stress of separation from SSC is immediate and profound, resulting in decreased physiologic stability and increased cortisol levels. If the baby must be transferred to another hospital, the baby will be most stable during transport if in SSC with the mother, father, or another primary caregiver. All electronic monitoring can and should be done during transport in SSC.

POSITIONING

The baby should be wearing only a diaper and a hat and placed in a prone position on the parent's bare chest. The baby's head should be turned to the side by about 45° with the chin slightly extended. The baby's limbs should be flexed and placed in SSC on the parent's chest with the baby's hands near his/her face. A warmed wrap or blanket should be secured around the baby and the parent to keep the baby in place for comfort and safety, even when the parent is sleeping. The wrap or blanket should be tucked under the baby's feet to provide a foot boundary that will simulate the walls of the uterus. Neither the mother nor the baby should ever be left unmonitored but rather should be monitored continuously and observed regularly for comfort, stability, and safety.

EQUIPMENT

An adult bed in the NICU is ideal for continuous or prolonged SSC. When a bed is not available or feasible, a comfortable reclining chair should be available. Rocking chairs are not suitable for prolonged SSC. They are usually not as comfortable as a reclining chair and can be unsafe when used with an intubated baby, as the rocking motion can lead to inadvertent extubation. If the NICU does not have private rooms, a privacy screen should be used during the transfer of the baby to the parent's exposed chest. A warm wrap designed for SSC or a blanket should be used to secure the baby to the parent's chest, so that the baby will be safe, even when the parent is sleeping. Clips can be used to secure lines and tubes. A mirror is useful for the parent to be able to view the baby's face.

DURATION

Continuous SSC is the developmental expectation of all newborns and where they are usually the most stable. SSC should continue unless the baby becomes unstable and all measures to stabilize the baby while in SSC have been unsuccessful. The most common reason for transient instability is positioning, so the baby's position should be checked and adjusted if needed. The baby's airway, ventilation tubing, and IV sites should also be evaluated as well as the need for oral or nasal suctioning. If the baby remains unstable with apnea, bradycardia, desaturations, or hypotension in spite of these adjustments, the baby should be returned to the bed for further

evaluation and treatment and returned to SSC again as soon as possible when the instability has resolved.

To provide continuous or prolonged SSC, parents must be supported physically, mentally, and emotionally. Parents will need to trade off and can share SSC with a limited number of primary care providers designated by the parents. An adult hospital bed placed next to the baby's monitoring or ventilator equipment is ideal. A comfortable reclining chair with good back support is required if a bed is not available. If no reclining chairs are available, at a minimum, good back support and a footstool should be provided.

STAFF EDUCATION

Staff education and training about SSC are essential for NICU staff from every discipline that will be interacting with babies and/or parents. Staff education should be provided in a variety of learning formats such as classroom, online, written, and simulation. The multiple, well-documented benefits of SSC for babies and parents such as warmth, physiologic stability, neurodevelopment, breastfeeding, bonding/attachment, and love should all be included. NICU staff from all disciplines should recognize the importance of their own attitudes about SSC and the vital role they play in actively encouraging parents to provide SSC for their preterm or sick baby. They should also understand the importance of good hand hygiene for themselves and the need to teach parents how to perform effective hand cleaning. Staff should also be proactive in ensuring a quietly healing environment that includes an absence of loud noises, bright lights, or noxious scents (including tobacco and strong fragrance).

All NICU staff who might assist in transferring a baby from the incubator to the parent's chest should have hands-on practice/simulations doing both standing and sitting transfers utilizing a doll with tubes and lines. Theoretical knowledge is not enough, and it is important that these techniques be practiced in order to ensure safety during the actual process. Staff should know practical ways to position the baby to support comfort and stability, including placing babies' hands near their face, providing foot support, using a firm but gentle touch with the whole hand (rather than fingertips), and encouraging parents to softly talk or sing to their babies.

Staff should be able to recognize preterm infant physiologic and behavioral signs of discomfort, stress, and dysregulation and should not rely solely on the monitor to assess instability. In this way, small adjustments can be made to help prevent escalation of a problem. Physiological signs of stress or dysregulation include sudden changes in heart rate, respiratory rate, or color, and behavioral signs of stress or dysregulation include hiccups, yawning, limb or finger extension, arching, hypotonia, or eye eversion. It is the staff's responsibility to share this information with parents, so they can be partners in supporting their baby's comfort and stability.

PARENT EDUCATION

Parents also need education related to SSC in a variety of learning formats about the many benefits of SSC for both the baby and the parent, as well as the importance of continuous or early, frequent, and prolonged SSC. Parents need to understand just how important they are for baby's physical stability as well as emotional and neurologic development. They need education on how to effectively clean their hands and how important this is to their immune-compromised baby. They can be partners in maintaining a quietly healing environment free of loud noises, bright lights, and noxious scents. They should be taught ways to support their baby's comfort and stability with positioning support and firm, whole-hand touch as well as softy talking or singing to their baby. By learning to recognize their baby's signs of stress or dysregulation and applying what they learn about supporting the baby's stability, they will be actively parenting their baby and will be seen by staff and themselves as active partners in their baby's care. If continuous SSC is not being done from birth, parents should have an opportunity to practice standing or sitting transfers with a doll if desired.

TRANSFERS

If the baby is not in continuous SSC, a transfer from the incubator to the parent's chest will be necessary. Transfers of very preterm babies require a team approach and should not be done without assistance from another staff. This is especially important if the baby is intubated or has an arterial line. A standing transfer is preferred if the parent is able to safely stand, as this technique maximizes the baby's contact with the parent and, therefore, maximizes the baby's stability. Whether doing a standing or sitting transfer, it is important that all movements during transfer be done very slowly and gently as this will greatly contribute to the baby's stability. If the baby is safely secured to the parent's chest, there is no reason the parent cannot fall asleep during SSC, but both parent and baby should be monitored continuously while in SSC and be observed regularly for comfort, stability, and safety.

SUMMARY

Skin-to-skin contact with mother (or primary caregiver) has been studied extensively in both animal and human models. The benefits are undeniable and implementation is relatively simple and cost effective. SSC is every new baby's birthright and, baring extreme circumstances, it is our privilege and responsibility to be sure they receive it.

REFERENCES

Als, H. (1984). *Manual for the naturalistic observation of the newborn (preterm and fullterm)*. Boston, MA: The Children's Hospital.

Arabadzisz, D., Diaz-Heijtz, R., Knuesel, I., Weber, E., Pilloud, S., Dettling, A. C., . . . Pryce, C. R. (2010). Primate early life stress leads to long-term mild hippocampal decreases in corticosteroid receptor expression. *Biological Psychiatry, 67*(11), 1106–1109. doi:10.1016/j.biopsych.2009.12.016

Bartocci, M., Winberg, J., Ruggiero, C., Bergqvist, L. L., Serra, G., & Lagercrantz, H. (2000). Activation of olfactory cortex in newborn infants after odor stimulation: A functional near-infrared spectroscopy study. *Pediatric Research, 48*(1), 18–23. doi:10.1203/00006450-200007000-00006

Bergman, N. (2014). The neuroscience of birth—And the case for zero separation. *Curationis, 37*(2), 1–4. doi:10.4102/curationis.v37i2.1440

Bergman, N., Linley, L., & Fawcus, S. (2004). Randomized controlled trial of skin-to-skin contact from birth versus conventional incubator for physiological stabilization in 1200- to 2199-gram newborns. *Acta Pædiatrica, 93*(6), 779–785. doi:10.1111/j.1651-2227.2004tb03018.x

Bergman, N. J. (2015). Neuroprotective core measures 1–7: Neuroprotection of skin-to-skin contact (SSC). *Newborn and Infant Nursing Reviews, 15*(3), 142–146. doi:10.1053/j.nainr.2015.06.006

Bramson, L., Lee, J. W., Moore, E., Montgomery, S., Neish, C., Bahjri, K., & Melcher, C. L. (2010). Effect of early skin-to-skin mother—infant contact during the first 3 hours following birth on exclusive breastfeeding during the maternity hospital stay. *Journal of Human Lactation, 26*(2), 130–137. doi:10.1177/0890334409355779

Chi Luong, K., Long Nguyen, T., Huynh Thi, D. H., Carrara, H. P., & Bergman, N. J. (2016). Newly born low birthweight infants stabilise better in skin-to-skin contact than when separated from their mothers: A randomised controlled trial. *Acta Pædiatrica, 105*(4), 381–390. doi:10.1111/apa.13164

Chia, P., Sellick, K., & Gan, S. (2006). The attitudes and practices of neonatal nurses in the use of kangaroo care. *The Australian Journal of Advanced Nursing, 23*(4), 20–27. Retrieved from http://www.ajan.com.au/Vol23/Vol23.4-3.pdf

Conde-Agudelo, A., & Diaz-Rossello, J. L. (2014). Kangaroo mother care to reduce morbidity and mortality in low birthweight infants. *Cochrane Database of Systematic Reviews*, (4), CD002771. doi:10.1002/14651858.CD002771.pub3

Craig, J. W., Glick, C., Phillips, R., Hall, S. L., Smith, J., & Browne, J. (2015). Recommendations for involving the family in developmental care of the NICU baby. *Journal of Perinatology, 35*, S5–S8. doi:10.1038/jp.2015.142

Feldman, R., Rosenthal, Z., & Eidelman, A. I. (2014). Maternal-preterm skin-to-skin contact enhances child physiologic organization and cognitive control across the first 10 years of life. *Biological Psychiatry, 75*(1), 56–64. doi:10.1016/j.biopsych.2013.08.012

Gallagher, W. (1992). Motherless child. *The Sciences, 32*(4), 12–15. doi:10.1002/j.2326-1951.1992.tb02399.x

Gray, L., Miller, L. W., Philipp, B. L., & Blass, E. M. (2002). Breastfeeding is analgesic in healthy newborns. *Pediatrics, 109*(4), 590. doi:10.1542/peds.109.4.590

Hall, S. L., Phillips, R., & Hynan, M. T. (2016). Transforming NICU care to provide comprehensive family support. *Newborn and Infant Nursing Reviews, 16*(2), 69–73. doi:10.1053/j.nainr.2016.03.008

Hofer, M. (1994). Hidden regulators mediating attachment, separation and loss. *Monographs of the Society for Research in Child Development, 59*, 192–207. doi:10.1111/j.1540-5834.1994.tb01285.x

Hofer, M. A. (2006). Psychobiological roots of early attachment. *Current Directions in Psychological Science, 15*(2), 84–88. doi:10.1111/j.0963-7214.2006.00412.x

Johnston, C. C., Stevens, B., Pinelli, J., Gibbins, S., Filion, F., Jack, A., . . . Veilleux, A. (2003). Kangaroo care is effective in diminishing pain response in preterm neonates. *Archives of Pediatrics and Adolescent Medicine, 157*(11), 1084–1088. doi:10.1001/archpedi.157.11.1084

Kirsten, G. F., Bergman, N. J., & Hann, F. M. (2001). Kangaroo mother care in the nursery. *Pediatric Clinics of North America, 48*(2), 443–452. doi:10.1016/S0031-3955(08)70036-1

Loman, M. M., & Gunnar, M. R. (2010). Early experience and the development of stress reactivity and regulation in children. *Neuroscience and Biobehavioral Reviews, 34*(6), 867–876. doi:10.1016/j.neubiorev.2009.05.007

Ludington-Hoe, S., Morgan, K., & Abouelfettoh, A. (2008). A clinical guideline for implementation of kangaroo care with premature infants of 30 or more weeks' postmenstrual age. *Advances in Neonatal Care, 8*(3S), S3–S23. doi:10.1097/01.ANC.0000324329.25734.60

Michelsson, K., Christensson, K., Rothganger, H., & Winberg, J. (1996). Crying in separated and non-separated newborns: Sound spectrographic analysis. *Acta Pædiatrica, 85*(4), 471–475. doi:10.1111/j.1651-2227.1996.tb14064.x

Mikiel-Kostyra, K., Mazur, J., & Boltruszko, I. (2002). Effect of early skin-to-skin contact after delivery on duration of breastfeeding: A prospective cohort study. *Acta Pædiatrica, 91*(12), 1301. doi:10.1111/j.1651-2227.2002.tb02824.x

Mooncey, S., Giannakoulopoulos, X., Glover, V., Acolet, D., & Modi, N. (1997). The effect of mother–infant skin-to-skin contact on plasma cortisol and β-endorphin concentrations in preterm newborns. *Infant Behavior and Development, 20*(4), 553–557. doi:10.1016/S0163-6383(97)90045-X

Morgan, B. (2013). *Biological embedding of early childhood adversity: Toxic stress and the vicious cycle of poverty in South Africa*. Retrieved from http://ilifalabantwana.co.za/wp-content/uploads/2017/06/Toxic-stress-and-the-vicious-cycle-of-poverty-in-South-Africa.pdf

Nyqvist, K. H. (2008). Early attainment of breastfeeding competence in very preterm infants. *Acta Pædiatrica, 97*(6), 776–781. doi:10.1111/j.1651-2227.2008.00810.x

Nyqvist, K. H., Anderson, G. C., Bergman, N., Cattaneo, A., Charpak, N., Davanzo, R., . . . Wiström, A. M. (2010). State of the art and recommendations. Kangaroo mother care: Application in a high-tech environment. *Breastfeeding Review, 18*(3), 21–28.

Nyqvist, K. H., & Engvall, G. (2009). Parents as their infant's primary caregivers in a neonatal intensive care unit. *Journal of Pediatric Nursing, 24*(2), 153–163. doi:10.1016/j.pedn.2008.07.006

Parmar, V. R., Kumar, A., Kaur, R., Parmar, S., Kaur, D., Basu, S., . . . Narula, S. (2009). Experience with kangaroo mother care in a neonatal intensive care unit (NICU) in Chandigarh, India. *Indian Journal of Pediatrics, 76*(1), 25–28. doi:10.1007/s12098-009-0024-2

Penalva, O., & Schwartzman, J. S. (2006). Descriptive study of the clinical and nutritional profile and follow-up of premature babies in a kangaroo mother care program. *Jornal de Pediatria, 82*(1), 33–39. doi:10.2223/JPED.1433

Reite, M., Seiler, C., & Short, R. (1978). Loss of your mother is more than loss of a mother. *The American Journal of Psychiatry, 135*(3), 370–371. doi:10.1176/ajp.135.3.370

Sabatini, M. J., Ebert, P., Lewis, D. A., Levitt, P., Cameron, J. L., & Mirnics, K. (2007). Amygdala gene expression correlates of social behavior in monkeys experiencing maternal separation. *The Journal of Neuroscience, 27*(12), 3295–3304. doi:10.1523/JNEUROSCI.4765-06.2007

Sanders, M. R., & Hall, S. L. (2018). Trauma-informed care in the newborn intensive care unit: promoting safety, security and connectedness. *Journal of Perinatology, 38*(1), 3–10. doi:10.1038/jp.2017.124

Shonkoff, J. P. (2010). Building a new biodevelopmental framework to guide the future of early childhood policy. *Child Development, 81*(1), 357–367. doi:10.1111/j.1467-8624.2009.01399.x

Shonkoff, J. P., Garner, A. S., Siegel, B. S., Dobbins, M. I., Earls, M. F., McGuinn, L., . . . Wood, D. L. (2012). The lifelong effects of early childhood adversity and toxic stress. *Pediatrics, 129*(1), e232–e246. doi:10.1542/peds.2011-2663

Sontheimer, D., Fischer, C. B., & Buch, K. E. (2004). Kangaroo transport instead of incubator transport. *Pediatrics, 113*(4), 920–923. doi:10.1542/peds.113.4.920

Uvnas-Moberg, K. (2003). *The oxytocin factor: Tapping the hormone of calm, love, and healing*. Cambridge, MA: Da Capo Press.

Wallin, L., Rudberg, A., & Gunningberg, L. (2005). Staff experiences in implementing guidelines for kangaroo mother care–a qualitative study. *International Journal of Nursing Studies, 42*(1), 61–73. doi:10.1016/j.ijnurstu.2004.05.016

Welch, M. G., Myers, M. M., Grieve, P. G., Isler, J. R., Fifer, W. P., Sahni, R., . . . Stark, R. I. (2014). Electroencephalographic activity of preterm infants is increased by Family Nurture Intervention: A randomized controlled trial in the NICU. *Clinical Neurophysiology, 125*(4), 675–684. doi:10.1016/j.clinph.2013.08.021

III

Developmental Care for the Sick and Preterm Infant

Caitlin Bradley and Christina Mahoney

INTRODUCTION

Temporary and permanent structural and functional limitations occur with prematurity and illness in the newborn period and are associated with morbidities such as positional deformities, cerebral palsy, cognitive issues, behavioral issues, inattention/hyperactivity, anxiety, social issues, emotional difficulties, and epilepsy (Glass et al., 2015). These morbidities increase in frequency and severity depending on diagnoses, gestational age at birth, and care management. Research demonstrates that developmental care is an effective method to support the premature and sick infant during a time of vital neurosensory development, leading to short- and long-term benefits, and perhaps diminishing morbidity (Altimier & Phillips, 2013, 2016; Cardin et al., 2015).

Since its inception in the 1970s, developmental care for the premature and sick infant has undergone significant evolution. The comprehensive benefits of developmental care are neuroprotective. Evidence demonstrates that neuronal cell death can be avoided, and the fragile brain can even heal with neuroprotective developmental care (Altimier & Phillips, 2013). The seven neuroprotective core measures used to frame this protocol are: (1) the healing environment, (2) partnering with families, (3) positioning and handling, (4) safeguarding sleep, and (5) minimizing stress and pain (6) protecting skin, and (7) optimizing nutrition (Altimier & Phillips, 2013). (For more information see Chapter 32, The Neonatal Intensive Care Unit [NICU] Environment).

NEUROPROTECTIVE CORE MEASURES

The Healing Environment

Altimier and Phillips (2013) define the healing environment as inclusive of the infants' total environment including the physical space they occupy, their safety, and sensory experiences. Ideally, the intrauterine environment integrates all these components, exposing the developing fetus to appropriate amounts of stimulus. The neurosensory system develops during the final 16 to 20 weeks of gestation; therefore, the development of the neurosensory system among premature infants is shaped by the NICU's ever-changing environmental and sensory stimuli. Instability in the NICU environment can be detrimental to the infant's developing neurosensory system (Graven & Browne, 2008). However, there are neuroprotective interventions that can be implemented by the multidisciplinary team and the infant's families that can mitigate the negative environmental and sensory stimuli and improve outcomes.

Physical space and ambient temperature are critical components to the general NICU environment. Traditional open-bay units cannot be tailored to an infant's individual needs, lack privacy, and prevent feelings of discharge readiness by family members (Meredith, Jnah, & Newberry, 2017; Winner-Stoltz et al., 2018). Inability to control temperature in the open-bay NICU design can result in hypo- or hyperthermia, increasing the infant's metabolic demand and impeding weight gain and healing. A neutral thermal environment (NTE) is one that leads to neither heat loss nor gain. Therefore, the environment should not increase the metabolic demand of the premature and sick infant. Monitoring temperature and maintaining ambient temperature is critical. Double-walled incubators are preferred to radiant warmers, as they perform several neuroprotective functions including reduction of convective heat loss, evaporative heat loss, and noise. Regardless of the exogenous heat source, temperature probes must be used to continuously monitor the infant's temperature. This serves several purposes: (1) the exogenous heat source can adapt to the infant's temperature, which prevents heat loss or gain, (2) reduction of hands-on, manual temperature checks, allowing clustered care, and (3) sleep disruptions to monitor temperature are minimized (Altimier, 2012).

NEUTRAL THERMAL ENVIRONMENT

Environmental temperature: 72°F to 78°F (22°C–26°C)
Infant temperature: 97.7°F to 99.5°F (36.5°C–37.5°C)

Source: From Altimier, L. B. (2012). Thermoregulation: What's new? What's not? *Newborn and Infant Nursing Reviews*, *12*(1), 51–63. doi:10.1053/j.nainr.2012.01.003

Inappropriate neurosensory stimuli can also alter development. The source of stimuli can be light, noise (sound), smell, taste, and/or touch. Excessive light in open-bay unit designs can lead to poor weight gain, eye damage, and sleep disruption and must be avoided (Meredith et al., 2017). In general, lighting should be limited to the guidelines found in Table III.1. When excess lighting is required for examinations and procedures, the infant's eyes must be shielded. This shielding can be accomplished using phototherapy goggles, a hat, or a soft washcloth. Further, dimming lights at night and providing brighter lighting during the day, as tolerated, is also recommended (Meredith et al., 2017; M. S. Rea & Figueiro, 2016).

The effect of noise on the developing brain has a dose–response relationship, with risks including interrupted sleep, stress, increased intracranial pressure, hearing loss, sleep disruption, and abnormal long-term behavior (Casavant, Bernier, Andrews, & Bourgoin, 2017; Edwards & Austin, 2016; Meredith et al., 2017). Approximately 25% of hearing loss identified during childhood is due to injury incurred during the intrapartum or perinatal period (Centers for Disease Control and Prevention, 2014). For NICU patients, a range of factors and exposures, including ischemia, infection, ototoxic medications, and others, represent risk factors for hearing loss (Stewart, Bentley, & Knorr, 2017). Modifiable risk factors include daily exposure to alarms, conversations, cellular telephones, and overhead announcements. The American Academy of Pediatrics (AAP) and the *Recommended Standards for Newborn ICU Design* recommend that mean noise levels in the NICU should not exceed 45 decibels; this level of noise is like the ambient noise in a quiet home or the level of noise experienced in light traffic (White, Smith, & Shepley, 2013).

Noxious smells and tastes represent another risk in neurosensory development for NICU patients. Examples of noxious smells include tobacco and strong perfumes. Commonly used NICU products that produce noxious smells and tastes include alcohol wipes and alcohol-based hand sanitizers (Altimier & White, 2019). Consequences of noxious smells and tastes include apnea, bradycardia, and tachypnea. Every effort should be made to minimize these life-threatening, exposure-elicited stress responses (Browne, 2008).

While there are many risks for the developing infant, evidence suggests that neuroprotective measures can improve care and reduce morbidity. Perhaps the intervention with the most potential for global improvement in neuroprotective care is modernizing the physical space. New NICU design and construction is focused on single-family rooms. Single-family rooms have many benefits for infants, their families, and the multidisciplinary team. Ambient temperature, light, and sound can be tailored for the infant's individual needs, to decrease stress and minimize sequela of negative stimuli (Meredith et al., 2017; Winner-Stoltz et al., 2018). Single-family rooms are reported to offer increased control of the environment without impeding the delivery of care (White, 2018). Single-family rooms provide private space for pumping breastmilk and quicker establishment of breastfeeding (Winner-Stoltz et al., 2018). Additionally, single-family rooms allow earlier independent functioning for the family and facilitate discharge readiness (Meredith et al., 2017; Watson, DeLand, Gibbons, York, & Robson, 2014).

Single-family room design is not only therapeutic for infants and families but is also an efficient workspace for the multidisciplinary team. Multidisciplinary teams express satisfaction with single-family rooms due to fewer interruptions in the delivery of care, which reduces errors (Winner-Stoltz et al., 2018).

TABLE III.1

LIGHTING STANDARDS RECOMMENDATIONS

Ambient lighting in the immediate care area	10–600 lux (e.g., dark to regular indoor lighting) Must have the ability to manually adapt lighting
Procedure lighting	2,000 lux (e.g., bright indoor lighting) Infant's eyes must be shielded
Ambient lighting in non-care areas	300 lux (e.g., dim indoor lighting)
Cyclic lighting	Windows with daylight access, and the ability to limit this light

Source: Rea, M. S., & Figueiro, M. G. (2016). The NICU lighted environment. *Newborn and Infant Nursing Reviews, 16*, 195–202. doi:10.1053/j.nainr.2016.09.009

Partnering With Families

The hospitalization of a newborn is often unexpected and a significant stressor to the family. Promoting an environment that fosters involvement, bonding, and education positively impacts both the infants and families (Craig et al., 2015). Family participation is the foundation to providing quality developmental care. Utilization of the family integrated care model supports family involvement in all aspects of their child's care through education, hands-on developmental care, and collaboration with the multidisciplinary team (O'Brien et al., 2013; Shoo & O'Brien, 2014). Programs should be in place to provide continuing education to staff on family-centered care practices and how to best support parents through education.

Education for parents begins on the first day of the NICU admission. Teaching families about their child's illness and care interventions empowers parents to make informed decisions for their child and conveys to them just how integral they are within the team (Maree & Downes, 2016). Staff should welcome families as the primary caregivers, answer questions, listen to concerns, and educate parents on the care of their infant (Altimier, Kenner, & Damus, 2015). Parents who feel included in their child's care will be more informed and become better advocates. Some NICUs have adopted parental involvement during team rounds, incorporating parents as a vital member of the team. Parents have reported positive benefits of being directly included in discussions and feel more knowledgeable about their child's care. Participation during rounds can lead to an increased understanding of their child's condition and can facilitate relationships with the healthcare team (Gustafson, LaBrecque, Graham, Tella, & Curley, 2016).

All members of the multidisciplinary team must aim to partner with families and provide a welcoming environment, with open visitation, and encourage interaction with their infants. It is important to develop a relationship of trust and support between healthcare staff and families. Strengthening these relationships has shown to reduce parental anxiety and can provide increased trust and confidence in the medical team (K. E. Rea, Rao, Hill, Saylor, & Cousino, 2018).

Facilitating skin-to-skin care (or kangaroo care) between the infant and family member is another way of integrating them into the care of their infant. Skin-to-skin care meets the environmental, proprioceptive (spatial awareness), and thermoregulatory needs of the premature and sick infant. It provides an ideal neutral thermal environment (NTE) and optimizes smell, taste, touch, and proprioception (Altimier & Phillips, 2016, 2018). Infants, wearing only a diaper, are placed on the bare chest of their family member. To minimize heat loss through skin that is not in contact with their

family member, gently warmed blankets are used to cover the infant's back and a hat is placed on his or her head.

When skin-to-skin care is not available or appropriate, and exogenous heat is required, family members can be encouraged to participate in care through other methods. Assist family members in the use of positional supports, a wearable blanket, or swaddling the infant. Providing the smell of family members can also be accomplished with the use of fabric items that have been held by family members.

Positioning and Handling

The gestational age and the severity of illness can necessitate medical interventions, procedures, frequent handling, and use of medical equipment that restricts proper positioning (Danner-Bowman & Cardin, 2015). Improper handling of premature and sick infants causes autonomic instability, as manifested by mottling, hiccupping, apnea, bradycardia, and oxygen desaturation. Improper or excessive handling may lead to poor weight gain secondary to excessive metabolic demands.

Preterm and sick infants must be handled using slow motion, while simultaneously maintaining the infant in a flexed/contained position. Staff should encourage hands-on care through skin-to-skin contact and proper positioning with guidance on infant behavioral cues and signs of stress. Research demonstrates that educating parents to identify stress signs reduces stress in their infants and is neuroprotective (Craig et al., 2015). Clustered-care or using the infant's wakeful cues to guide timing of handling is also important to minimize sleep interruptions.

Preventing problems associated with improper positioning of infants is often difficult and hindered by the patient's condition. Similar to handling issues, improper positioning can lead to both short-term and long-term consequences. Short-term consequences from improper positioning of infants include discomfort, poor sleep, limb and joint deformities, autonomic instability, poor weight gain, and positional head deformities (Hunter, Lee, & Altimier, 2015; Jeanson, 2013). The most prevalent head shape deformities among NICU patients are scaphocephaly, plagiocephaly, and brachycephaly. Examples of long-term implications of positional deformities include poor parent–infant attachment, bullying, and neurobehavioral problems. These short- and long-term consequences are also detrimental to the neurodevelopment of infants, placing them at risk for delayed milestones (Danner-Bowman & Cardin, 2015).

Preterm and critically ill infants may remain inpatient for prolonged periods; thus, positioning interventions require the attention of all caregivers. Interventions to prevent position-associated problems include frequent position changes and approaching the infant from all sides. Assisting infants to remain in a flexed, midline, and contained position can be achieved with the aid of positioning devices. Supportive positioning can promote comfort, respiratory function, and aid in musculoskeletal integrity (Danner-Bowman & Cardin, 2015). One method to support positioning is swaddling, which improves muscle tone and sleep quality, and decreases physiologic stress (Kitase et al., 2017).

With respect to head shape deformities, the correction depends upon the severity of deformity. Similar to prevention methods for other positioning problems, mild head shape deformities can be corrected through changes in position and approaching the infant from all sides. For more significant deformities, therapeutic positioners that provide support to the infant's developing head can aid correction without negatively impacting the infant's physiologic condition (Knorr, Gauvreau, Porter, Serino, & DeGrazia, 2016). When cranial support apparatuses are used in conjunction with other positioning aids, such as swaddling and boundaries, containment and proper body alignment can also be achieved.

Positioning and handling guidelines to support the development of premature and hospitalized infants should be adopted by all caregivers. Providing infants with skillful, supportive positioning and aiming to minimize handling throughout their hospital admission can promote sleep, self-regulation, growth, and weight gain, which will optimize brain development (Altimier & Phillips, 2013). Positioning tools can be used to encourage staff consistency in positioning babies in the NICU (Jeanson, 2013; Spilker, Hill, & Rosenblum, 2016).

Encouraging interaction between the infant and family member while the infant is prone and awake is also shown to be beneficial (Danner-Bowman & Cardin, 2015). The multidisciplinary team should provide families instruction and demonstration in proper handling and positioning of the infants. Through education, families can transfer what is learned in the hospital setting to their homes and optimize both physical and neurodevelopmental outcomes of their child (Danner-Bowman & Cardin, 2015). The AAP (2016) *Back to Sleep* guidelines should be implemented when developmentally appropriate and prior to hospital discharge (see the section on Safeguarding Sleep later in this chapter).

Therapeutic Positioning and Safe Sleep

Therapeutic positioning provides support to the hospitalized infant by facilitating physiologic stability, growth, and musculoskeletal and brain development (Altimier & Phillips, 2016). Devices used to provide therapeutic positioning promote proper body alignment and containment, without restricting spontaneous movement (Altimier & Phillips, 2013). The appropriate timing for the transition from NICU therapeutic positioning to safe sleep for Sudden Infant Death Syndrome (SIDS) prevention must be considered prior to discharge to home. Transitioning from therapeutic NICU positioning to safe sleep practice is a multidisciplinary decision that includes the family.

The criteria that an infant is medically stable and reaching appropriateness for safe sleep readiness include greater than 34 weeks corrected gestational age, off positive pressure ventilation, and able to regulate temperature in an open crib (Table III.2). Table III.3 includes safe sleep practice recommendations including supine, flat head of the bed, and more. Educating families about safe sleep is incredibly important; NICU patients are specifically at high risk for SIDS. Education coupled with healthcare providers serving as role models for safe sleep practices can improve parental compliance, which is also an issue for families whose infants had been in the NICU (Moon, Darnall, Feldman-Winter, Goodstein, & Hauck, 2016).

Parents should receive updated AAP safe sleep guidelines (see Table III.3; Moon et al., 2016) and practice/demonstrate safe sleep positioning a minimum of 5 to 7 days prior to discharge (Altimier et al., 2015). Beyond safe sleep positioning, secondhand smoke must be avoided, as it increases the risk for SIDS, independent of safe sleep positioning. Additionally, maternal alcohol and drug abuse also increases the risk of SIDS. Families should be screened and counseled to avoid tobacco, alcohol, and drugs. Breastfeeding should be encouraged because it is known to reduce the risk of SIDS regardless of gestational age.

TABLE III.2

INITIATION OF SAFE SLEEP

34 weeks corrected gestational age
No longer requiring positive pressure ventilation
Open crib

TABLE III.3

SAFE SLEEP PRACTICE RECOMMENDATIONS

Supine positioning for sleep
Sleep surface must be firm, flat mattress with a fitted sheet, and no other bedding or soft objects
Breastfeeding should be encouraged
Sleep location should be close to the parents, but a separate surface
No cobedding
Consider use of a pacifier during sleep times
Avoid overheating
Immunize according to the AAP and CDC guidelines
Encourage awake, observed tummy time
Discontinue swaddling while sleeping when the infant can roll
Maternal smoking and alcohol must be avoided

Source: From Moon, R. Y., Darnall, R. A., Feldman-Winter, L., Goodstein, M. H., & Hauck, F. R. (2016). SIDS and other sleep-related infant deaths: Evidence base for 2016 updated recommendations for a safe infant sleeping environment. *Pediatrics, 138*, e1–e34. doi:10.1542/peds.2016-2940

TABLE III.4

STRESS SIGNS AUTONOMIC, MOTOR, AND STATE SYSTEM

Autonomic System	
Respiratory	Tachypnea, irregular breathing pattern, apnea, bradypnea, sighing, gasping
Color	Pale, mottling, plethoric, cyanosis
Visceral	Multiple coughs, sneezes, or yawns, hiccupping, gagging, grunting, straining, and vomiting
Related motor	Tremors, startles, twitching
Motor System	
Tone	Hypertonia, hypotonia, hyperflexion
Posture	Unable to maintain flexion, alignment
Level of activity	Frequently moving, or no movement
State System	
Sleep	Restless, low cries, responsive to environment
Awake	Unfocused, gaze aversion, hyperalert with wide eyes, crying, eyes closed to avoid gaze, poor sleep times, difficult to console

Sources: From Brandon, D., Ryan, D., & Barnes, A. (2007). Effect of environmental changes on noise in the NISU/SCN. *Neonatal Network, 26*, 213–218. doi:10.1891/0730-0832.26.4.213; Spruill Turnage, C., & Papile, L. (2012). Developmentally supportive care. In J. Cloherty, E. Eichenwald, A. Hansen, & A. Stark (Eds.), *Manual of neonatal care* (7th ed., pp. 166–177). Philadelphia, PA: Lippincott Williams & Wilkins; White, R. (2011). The newborn intensive care unit environment of care: How we got here, where we're headed, and why. *Seminars in Perinatology, 35*, 2–7. doi:10.1053/j.semperi.2010.10.002

Minimizing Stress and Pain

Symptoms of stress and pain among NICU patients have long been established (see Table III.4). Pain assessments in neonates are challenging as neonates display a wide range of responses; stress and pain symptoms change as gestational age increases (Montirosso & Provenzi, 2015). Minimization of stress and pain plays a significant role in neuroprotection. While the signs in Table III.4 have long been recognized, they can be difficult to discern considering other clinical scenarios including prematurity, sepsis, respiratory distress, apnea of prematurity, feeding intolerance, and others.

Chronic stress and pain are deleterious to optimal neurodevelopment, and even have a negative impact on the stress response later in life (Montirosso & Provenzi, 2015). For preterm and sick infants, stress originates from several sources: separation from the family, painful procedures, noise, tactile stimulation, and more (Alvarez-Garcia, Fornieles-Deu, Costas-Moragas, & Botet-Mussons, 2014). From a physiologic perspective, there are short- and long-term effects of stress and pain (Anand, 2000). Short-term effects of stress and pain include cortisol release and binding onto glucocorticoid receptors (Montirosso & Provenzi, 2015). When stress and pain are chronically experienced, glucocorticoid receptors become saturated, leading to loss of dendritic arborization, negative synaptogenesis, and ultimately decreased cerebral volume. These physiologic findings lead to increasingly poor neurodevelopmental outcomes including motor and cognitive deficiencies. Prevention of stress is accomplished using the neuroprotective interventions previously discussed, including nonnutritive sucking, clustered care, midline positioning, and skin-to-skin care as examples. These techniques should be used prophylactically when performing any procedures on NICU patients, including routine care. Stress can be eliminated or reduced with preventive strategies. When caregivers recognize stress signs, rectifying the infant's experience can limit or prevent negative neurodevelopmental consequences.

Pain management is achieved with a multitude of interventions, depending on the source and severity of pain. Breastfeeding, nonnutritive sucking, skin-to-skin care, facilitated tucking, swaddling, and administration of sucrose are effective for mild to moderate pain. Medications, such as morphine or fentanyl, can also be used for more severe pain, in addition to other nonpharmacologic methods such as swaddling and nonnutritive sucking. Recognizing and treating pain in NICU patients is critical to avoid excess metabolic demands and promote physiologic stability.

Safeguarding Sleep

Sleep is vital to brain development. Proper sleep cycles are necessary for temperature regulation, energy storing, learning, and memory formation (Lacina et al., 2015). Sleep interruptions lead

to increased learning disabilities and behavioral issues, and decreased brain volume (Altimier & Phillips, 2016).

The NICU environment can create interference to sleep cycles by exposure to excessive lighting, elevated noise levels, and frequent handling for cares or procedures (Lacina et al., 2015). Minimizing sleep interruptions is achieved by adjustments to the NICU environment and, when able, by limiting caregiver interruptions. Sleep can be improved using several methods. Interventions such as use of single-family rooms, appropriate lighting and noise, clustered-care, and using individual infant cues are important strategies to minimize sleep interruptions. Interventions to minimize sleep interruptions should also include education for the family.

Along with the staff, the family members can be taught to use positioning aids such as swaddling or conformational positioners, fluidized neonatal pillows, or containment techniques and boundaries. In a study evaluating the sleep of infants using a conformational positioner in comparison to standard positioning, the use of a positioning pillow significantly improved sleep quality (Lacina et al., 2015). The infant's individual awake and sleep periods also improves sleep quality. To further enhance this intervention, adapting the caregiver's approach based on the infant's stress signs decreases sleep disturbances (Altimier et al., 2015). When infants require incubators for thermoregulation, incubator covers improve sleep quality and should be used in conjunction with lighting guidelines found in Table III.1. Also, skin-to-skin contact, proper positioning, and handling all benefit sleep and are neuroprotective.

Protecting skin

Skin has many important functions: thermoregulation, balance of fluid and electrolytes, immune protection, and sense of touch. Premature skin structure is immature when compared to full-term infants in several ways that predispose them to greater risk for infection and poor thermoregulation. The premature infant's skin is underdeveloped and has higher body surface area to weight. Supportive care during skin development is crucial to alleviate poor thermoregulation and risk of infection (Visscher, Adam, Brink, & Odio, 2015; Visscher & Narendran, 2014).

The acid mantle is a critical part of the skin's defense from pathogens. However, maturation and proper function of the acid mantle is delayed up to 8 weeks among premature infants (Visscher et al., 2009). While the skin of full-term infants can take up to 1 week to mature, the skin of premature infants can take up to 3 weeks (Altimier & Phillips, 2013). During this time, they are vulnerable to infection via their skin. While there is no way to hasten this process, caregivers can avoid further disruption. For example, bathing should not be done if the infant has gelatinous skin. After the skin matures enough for bathing, it should be done only one to two times per week, and only with water (Allwood, 2011).

Thermoregulation is another critical function of the skin. Due to the lack of maturity and large body surface area to weight, transepidermal water loss (TEWL), heat maintenance, weight loss, and hypothermia are risks to the premature infant. To provide a neutral thermal environment and reduce TEWL, a polyurethane wrap is used in the delivery room for very preterm infants (Allwood, 2011; Altimier, 2012). In the NICU, double-walled incubators provide heat and have the capacity to provide humidity. While the use of emollient creams was routine in the past, the evidence for the effectiveness of this practice is lacking. Further, they have been linked to nosocomial bacterial and fungal infections; therefore, their routine use is discouraged (Allwood, 2011; Saiman, 2006).

Optimizing Nutrition

Growth is critical for infants. For infants in the NICU, enteral nutrition may not be appropriate depending on clinical condition. For these infants, parenteral nutrition is necessary. Central lines are used to deliver parenteral nutrition; however, there is a risk of central line associated bloodstream infections (CLABSIs). The earliest attainment of full enteral feedings, and earliest removal of central lines, reduces the risk for infection. The benefits of breastfeeding for infants have long been documented and include ease of digestibility, earlier attainment of full enteral feedings, and reduced risk for infection (short-term and long-term; Hawes & Lee, 2018). While the type of enteral feeding is important in achievement of full feedings and weight gain, the use of feeding guidelines can also improve earlier attainment of full feedings without increased risk for necrotizing enterocolitis (Culpepper, Hendrickson, Marshall, Benes, & Grover, 2017).

SUMMARY

Common threads of the seven neuroprotective core measures presented in this chapter simultaneously aid caregivers as they endeavor to support the neurodevelopment of premature and sick infants. As an example, skin-to-skin care offers many benefits including supporting the healing environment (temperature, touch, and proprioception); smell and taste; partnering with families, positioning, and handling; safeguarding sleep; and minimizing stress and pain (Altimier & Phillips, 2016). Skin-to-skin care also supports breastfeeding, which improves nutrition for the premature and sick infant.

Neuroprotective care has been critically important in achieving improved outcomes for fragile infants. Promoting neuroprotection for premature and sick infants requires skillful care and a multidisciplinary team approach. The multidisciplinary care team is inclusive of family members, which provides the most long-term benefits. Individualized care guided by infant's cues is critical. The future of neuroprotective developmental care includes researching developmental and family outcomes.

REFERENCES

Allwood, M. (2011). Skin care guidelines for infants aged 23–30 weeks' gestation: A review of the literature. *Neonatal, Paediatric and Child Health Nursing, 14*, 20–27.

Altimier, L., Kenner, C., & Damus, K. (2015). The Wee Care Neuroprotective NICU Program (Wee Care): The effect of a comprehensive developmental care training program on seven neuroprotective core measures for family-centered developmental care of premature neonates. *Newborn and Infant Nursing Reviews, 15*, 6–16. doi:10.1053/j.nainr.2015.01.006

Altimier, L., & Phillips, R. (2013). The neonatal integrative developmental care model: Seven neuroprotective core measures for family-centered developmental care. *Newborn and Infant Nursing Reviews, 13*, 9–22. doi:10.1053/j.nainr.2012.12.002

Altimier, L., & Phillips, R. (2016). The neonatal integrative developmental care model: Advanced clinical applications of the seven core measures for neuroprotective family-centered developmental care. *Newborn and Infant Nursing Reviews, 16*(4), 230–244. doi:10.1053/j.nainr.2016.09.030

Altimier, L., & Phillips, R. (2018). Neuroprotective care of extremely preterm infants in the first 72 hours after birth. *Critical Care Nursing Clinics of North America, 30*(4), 563–583. doi:10.1016/j.cnc.2018.07.010

Altimier, L. B. (2012). Thermoregulation: What's new? What's not? *Newborn and Infant Nursing Reviews, 12*(1), 51–63. doi:10.1053/j.nainr.2012.01.003

Alvarez-Garcia, A., Fornieles-Deu, A., Costas-Moragas, C., & Botet-Mussons, F. (2014). Maturational changes associated with neonatal stress in preterm infants hospitalized in the NICU. *Journal of Reproductive and Infant Psychology, 32*, 412–422. doi:10.1080/02646838.2014.937411

American Academy of Pediatrics. (2016). American Academy of Pediatrics announces new safe sleep recommendations to protect against SIDS, sleep-related deaths. Retrieved from https://www.aap.org/en-us/about-the-aap/aap-press-room/Pages/American-Academy-of-Pediatrics-Announces-New-Safe-Sleep-Recommendations-to-Protect-Against-SIDS.aspx

Anand, K. S. (2000). Pain, plasticity, and premature birth: A prescription for permanent suffering? *Nature Medicine, 6*, 971–973. doi:10.1038/79658

Brandon, D., Ryan, D., & Barnes, A. (2007). Effect of environmental changes on noise in the NISU/SCN. *Neonatal Network, 26*, 213–218. doi:10.1891/0730-0832.26.4.213

Browne, J. V. (2008). Chemosensory development in the fetus and newborn. *Newborn and Infant Nursing Reviews, 8*, 180–186. doi:10.1053/j.nainr.2008.10.009

Cardin, A., Rens, L., Stewart, S., Danner-Bowman, K., McCarley, R., & Kopsas, R. (2015). Neuroprotective core measures 1–7: A developmental care journey: Transformations in NICU design and caregiving attitudes. *Newborn and Infant Nursing Reviews, 15*, 132–141. doi:10.1053/j.nainr.2015.06.007

Casavant, S. G., Bernier, K., Andrews, S., & Bourgoin, A. (2017). Noise in the neonatal intensive care unit: What does the evidence tell us? *Advances in Neonatal Care, 17*, 265–273. doi:10.1097/ANC.0000000000000402

Centers for Disease Control and Prevention. (2014). 2014 Data. Retrieved from https://www.cdc.gov/hearingloss/default.html

Craig, J. W., Glick, C., Phillips, R., Hall, S. L., Smith, J., & Brown, J. (2015). Recommendations for involving the family in developmental care of the NICU baby. *Journal of Perinatology, 35*, S5–S8. doi:10.1038/jp.2015.142

Culpepper, C., Hendrickson, K., Marshall, S., Benes, J., & Grover, T. (2017). Implementation of feeding guidelines hasten the time to initiation of enteral feeds and improves growth velocity in very low birth weight infants. *Advances in Neonatal Care, 17*, 139–145. doi:10.1097/ANC.0000000000000347

Danner-Bowman, K., & Cardin, A. D. (2015). Neuroprotective core measure 3: Positioning & handling—A look at preventing positional plagiocephaly. *Newborn and Infant Nursing Reviews, 15*, 111–113. doi:10.1053/j.nainr.2015.06.009

Edwards, A. D., & Austin, T. (2016). Noise in the NICU: How prevalent is it and is it a problem? *Infant, 12*, 161–165. Retrieved from http://www.infantjournal.co.uk/pdf/inf_071_rev.pdf

Glass, H. C., Costarino, A. T., Stayer, S. A., Brett, C., Cladis, F., & Davis, P. J. (2015). Outcomes for extremely premature infants. *Anesthesia and Analgesia, 120*, 1337–1351. doi:10.1213/ANE.0000000000000705

Graven, S. N., & Browne, J. V. (2008). Sensory development in the fetus, neonate, and infant: Introduction and overview. *Newborn and Infant Nursing Review, 8*, 169–172. doi:10.1053/j.nainr.2008.10.007

Gustafson, K. W., LaBrecque, M. A., Graham, D. A., Tella, N. M., & Curley, M. A. (2016). Effect of parent presence during multidisciplinary rounds on NICU-related parental stress. *Journal of Obstetrics, Gynecologic, and Neonatal Nursing, 45*, 661–670. doi:10.1016/j.jogn.2016.04.012

Hawes, J. A., & Lee, K.-S. (2018). Reduction in central line-associated bloodstream infections in a NICU: Practical lessons for its achievement and sustainability. *Neonatal Network, 37*, 105–115. doi:10.1891/0730-0832.37.2.105

Hunter, J., Lee, A., & Altimier, L. (2015). Neonatal intensive care unit. In J. Case-Smith & J. C. O'Brien (Eds.), *Occupational therapy for children and adolescents* (7th ed., pp. 595–635). St. Louis, MO: Mosby, Elsevier.

Jeanson, E. (2013). One-to-one bedside nurse education as a means to improve positioning consistency. *Newborn and Infant Nursing Reviews, 13*, 27–30. doi:10.1053/j.nainr.2012.12.004

Kitase, Y., Sato, Y., Takahashi, H., Shimizu, M., Ishikawa, C., Yamamoto, H., & Hayakawa, M. (2017). A new type of swaddling clothing improved development of preterm infants in neonatal intensive care units. *Early Human Development, 112*, 25–28. doi:10.1016/j.earlhumdev.2017.06.005

Knorr, A., Gauvreau, K., Porter, C. L., Serino, E., & DeGrazia, M. (2016). Use of the cranial cup to correct positional head shape deformities in hospitalized premature infants. *Journal of Gynecologic and Neonatal Nursing, 45*, 542–552. doi:0.1016/j.jogn.2016.03.141

Lacina, L., Casper, T., Dixon, M., Harmeyer, J., Haberman, B., Alberts, J. R., . . . Visscher, M. O. (2015). Behavioral observation differentiates the effects of an intervention to promote sleep in premature infants: A pilot study. *Advances in Neonatal Care, 15*, 70–76. doi:10.1097/ANC.0000000000000134

Maree, C., & Downes, F. (2016). Trends in family-centered care in neonatal intensive care. *The Journal of Perinatal and Neonatal Nursing, 30*, 265–269. doi:10.1097/JPN.0000000000000202

Meredith, J. L., Jnah, A., & Newberry, D. (2017). The NICU environment: Infusing single-family room benefits into the open-bay setting. *Neonatal Network, 36*, 69–76. doi:10.1891/0730-0832.36.2.69

Montirosso, R., & Provenzi, L. (2015). Implications of epigenetics and stress regulation on research and developmental care of preterm infants. *Journal of Obstetric, Gynecologic, and Neonatal Nursing, 44*, 174–182. doi:10.1111/1552-6909.12559

Moon, R. Y., Darnall, R. A., Feldman-Winter, L., Goodstein, M. H., & Hauck F. R. (2016). SIDS and other sleep-related infant deaths: Evidence base for 2016 updated recommendations for a safe infant sleeping environment. *Pediatrics, 138*, e1–e34. doi:10.1542/peds.2016-2940

O'Brien, K., Bracht, M., Macdonell, K., McBride, T., Robson, K., O'Leary, L., . . . Lee, S. K. (2013). A pilot cohort analytic study of family integrated care in a Canadian neonatal intensive care unit. *BMC Pregnancy Childbirth, 13*(Suppl. 1), S12. doi:10.1186/1471-2393-13-S1-S12

Rea, K. E., Rao, P., Hill, E., Saylor, K. M., & Cousino, M. K. (2018). Families' experiences with pediatric family-centered rounds: A systematic review. *Pediatrics, 141*, 1–15. doi:10.1542/peds.2017-1883

Rea, M. S., & Figueiro, M. G. (2016). The NICU lighted environment. *Newborn and Infant Nursing Reviews, 16*, 195–202. doi:10.1053/j.nainr.2016.09.009

Saiman, L. (2006). Strategies for prevention of nosocomial sepsis in the neonatal intensive care unit. *Current Opinion in Pediatrics, 18*, 101–106. doi:10.1097/01.mop.0000193300.25141.c5

Shoo, K. L., & O'Brien, K. (2014). Parents as primary caregivers in the neonatal intensive care unit. *Canadian Medical Association Journal, 186*, 845–847. doi:10.1503/cmaj.130818

Spilker, A., Hill, C., & Rosenblum, R. (2016). The effectiveness of a standardised positioning tool and bedside education on the developmental positioning proficiency of NICU nurses. *Intensive and Critical Care Nursing, 35*, 10–15. doi:10.1016/j.iccn.2016.01.004

Spruill Turnage, C., & Papile, L. (2012). Developmentally supportive care. In J. Cloherty, E. Eichenwald, A. Hansen, & A. Stark (Eds.), *Manual of neonatal care* (7th ed., pp. 166–177). Philadelphia, PA: Lippincott Williams & Wilkins.

Stewart, J. E., Bentley, J., & Knorr, A. (2017). Chapter 68: Hearing loss in neonatal intensive care unit graduates. In E. Eichenwald, A. Hansen, C. Martin, & A. Stark (Eds.), *Cloherty and Stark's manual of neonatal care* (8th ed., pp. 993–999). Philadelphia, PA: Lippincott Williams & Wilkins.

Visscher, M., Adam, R., Brink, S., & Odio, M. (2015). Newborn infant skin: Physiology, development, and care. *Clinics in Dermatology, 33*(3), 271–280. doi:10.1016/j.clindermatol.2014.12.003

Visscher, M., & Narendran, V. (2014). Neonatal infant skin: Development, structure and function. *Newborn and Infant Nursing Reviews, 14*, 135–141. doi:10.1053/j.nainr.2014.10.004

Visscher, M., Odio, M., Taylor, T., White, T., Sargent, S., Sluder, L., . . . Bondurant, P. (2009). Skin care in the NICU patient: Effects of wipes versus cloth and water on stratum corneum integrity. *Neonatology, 96*, 226–234. doi:10.1159/000215593

Watson, J., DeLand, M., Gibbons, S., York, E., & Robson, K. (2014). Improvements in staff quality of work life and family satisfaction following the move to single-family room NICU design. *Advances in Neonatal Care, 14*, 129–136. doi:10.1097/ANC.0000000000000046

White, R. D. (2011). The newborn intensive care unit environment of care: How we got here, where we're headed, and why. *Seminars in Perinatology, 35*, 2–7. doi:10.1053/j.semperi.2010.10.002

White, R. D. (2018). Defining the optimal sensory environment in the NICU: An elusive task. *Acta Paediatrica, 107*(7), 1112. doi:10.1111/apa.14296

White, R. D., Smith, J. A., & Shepley, M. M. (2013). Recommend standards for newborn ICU design, eighth edition. *Journal of Perinatology, 33*, S2–S16. doi:10.1038/jp.2013.10

Winner-Stoltz, R., Lengerich, A., Hench, A. J., O'Malley, J., Kjelland, K., & Teal, M. (2018). Staff nurse perceptions of open-pod and single family room NICU designs on work environment and patient care. *Advances in Neonatal Care, 18*, 189–198. doi:10.1097/ANC.0000000000000493

Neonatal Transport

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IV

INTRODUCTION

It has been estimated that there are over 65,000 transports of critically ill neonates in the United States each year (Karlsen, Trautman, Price-Douglas, & Smith, 2011). Neonatal transports have been described as a high-risk service due to the types of patients transported, the different environments the transport team must function in at each referring facility, the transport equipment itself, the mode of transportation, and the level of responsibility the transport team must assume as representatives of the receiving facility (Bouchut, Van Lancker, Chritin, & Gueugniaud, 2011; Cornette, 2004a; Dulkerian, Douglas, & Taylor, 2011; Fenton, Leslie, & Skeoch, 2004; Insoft & Schwartz, 2015; Kilpatrick, Papile, & Macones, 2017; Leppälä, 2010). For the most part, neonatal transports represent a low-volume, high-acuity aspect of neonatal intensive care (Duby et al., 2018).

While in the process of providing expert care and stabilization to the neonate, members of the transport team are also expected to provide education to the team at the referring facility and communicate with the family in a manner that will form the basis of parent and family involvement in the care of their infant (Duritza, 2009; Hawthorne & Killen, 2006; Hogan & Logan, 2004; Macnab, Richards, & Green, 1999; Mullaney, Edwards, & DeGrazia, 2014; Steeper, 2002).

REGIONALIZATION OF NEONATAL CARE

The 1976 March of Dimes publication *Toward Improving the Outcome of Pregnancy, Recommendations for the Regional Development of Maternal and Neonatal Health Services* described the development of a regionalized perinatal healthcare system (Little, Horbar, Wachtel, Gluck, & Muri, 2010). The underlying concept is to ensure effective and efficient patient flow with safe and quality care throughout the regional system (Kilpatrick et al., 2017; Robles et al., 2017; Rochefort & Lamothe, 2011; Staebler, 2011; Warner, Altimier, & Imhoff, 2002). These systems are generally defined geographically and within each geographic region are facilities that provide varying levels of neonatal care, designated as Level I, Level II, Level III, or Level IV. The AAP Committee on Fetus and Newborn (Barfield et al., 2012) and AAP and ACOG (Kilpatrick et al., 2017) have defined these four levels of care as described in Box IV.1. Facilities that provide Level III and IV care are also referred to as tertiary facilities or centers (Chang, Berry, Jones, & Sivasangari, 2015). Any facility that cares for neonates, no matter what their designated level is, is expected to be capable of providing neonatal resuscitation and stabilizing an ill neonate until a transport team arrives to assume care (Barfiled et al., 2012). For the most part, tertiary facilities assume the responsibility of providing interfacility neonatal transports and outreach education for the regional program.

STABILIZATION BY THE REFERRING FACILITY

It is preferable that identified high-risk neonates be born at a tertiary center, if that level of care is anticipated. However, the birth of an ill neonate requiring transport will be unexpected in most cases and the local team must be able to quickly recognize this need and provide the appropriate initial care (Fenton et al., 2004). The first step in the transport process is recognizing the neonate who requires care at a higher level facility. This is especially true for very low birth weight (VLBW) infants who have a much higher risk of morbidity and mortality if born at a referring hospital (Barfield et al., 2012; Chang et al., 2015; Kilpatrick et al., 2017; McNamara, Mak, & Whyte, 2005; Robles et al., 2017). A goal of *Healthy People 2020* (Healthy People 2030, 2019) is to reduce the percentage of births of VLBW infants outside of a Level III or IV facility to less than 17%.

There are programs available, such as PCEP® (Sinkin & Chisholm, 2016), S.T.A.B.L.E.® (Karlsen, 2017), and ACoRN® (www.acornprogram.net) that can be used as educational resources to train staff to care for unexpectedly ill neonates. Most regional programs will support one or two of these programs and the Level III or IV unit should actively participate in training staff at the referring facilities to recognize and begin to stabilize the unexpectedly ill neonate.

Once a neonate had been identified as needing transport, the nurse practitioner, physician assistant, or attending physician should contact the tertiary center to begin the transport process. While waiting for the transport team to arrive, the referring team should continue with the stabilization process they have already begun, paying particular attention to thermoregulation, glucose homeostasis, maintaining oxygenation and ventilation, establishing

Box IV.1

LEVELS OF NEONATAL CARE

Level I—Newborn Nursery

- Provide care to newborns >35 weeks' gestation that are physiologically stable

Level II—Special Care Nursery

- Provide care to stable or moderately ill born at >32 weeks' gestation and weigh ≥1,500 g with physiologic immaturity
- Provide convalescent care to neonates that have been in a tertiary unit
- Provide continuous positive airway pressure
- Provide mechanical ventilation for up to 24 hours

Level III—Neonatal Intensive Care

- Provide care for extremely high-risk and critically ill newborns
- Provide comprehensive care for neonates <32 weeks' gestation and/or weigh <1,500 g
- Provide conventional mechanical ventilation
- Provide high-frequency ventilation and inhaled nitric oxide
- On-site accessibility to pediatric subspecialists

Level IV—Regionalized Neonatal Intensive Care

- Provide Level III NICU care
- Provide ECMO therapy
- Repair complex cardiac abnormalities requiring cardiopulmonary bypass

ECMO, extracorporeal membrane oxygenation; NICU, neonatal intensive care unit.

Sources: Barfield, W. D., Papile, L.-A., Baley, J. E., Benitz, W., Cummings, J., Carlo, W. A., . . . Watterberg, K. L. (2012). Policy statement: Levels of neonatal care. *Pediatrics, 130*(3), 587–597. doi:10.1542/peds.2012-1999; Kilpatrick, S. J., Papile, L.-A., & Macones, G. A. (Eds.). (2017). *Guidelines for perinatal care* (8th ed.). Elk Grove Village, IL: American Academy of Pediatrics.

vascular access if necessary, and initiating antibiotic treatment if clinically indicated. In addition, the referring team should continue to be in contact with the tertiary center while the transport team is enroute if the neonate deteriorates or if any new issues are identified (Cornette, 2004b; Das & Leuthner, 2004; Stroud et al., 2013; Wright, 2000).

THE NEONATAL TRANSPORT PROGRAM

The AAP Section of Transport Medicine (Insoft & Schwartz, 2015) has stated that neonatal transports require "A qualified, highly trained and well-prepared and equipped team" (p. 1). It is generally the responsibility of the tertiary center of the regional system to provide the neonatal transport service. The transport team should serve as an extension of the unit the neonate is going to and provide that level of care at the referring facility (Insoft & Schwartz, 2015; Messner, 2011; Stroud et al., 2013). The neonatal transport program should be tailored to meet the needs identified by the entire regional program. There are specific elements that should be part of every transport program, including an identified medical director and a neonatal or perinatal coordinator. In addition to providing neonatal transports, the regional program should have an educational mission and have a process for quality assurance for the transport team, the tertiary center, and the other facilities in the region (Cornette, 2004a; Insoft & Schwartz, 2015; Kilpatrick et al., 2017; Lupton & Pendray, 2004; National Association of Neonatal Nurses [NANN], 2010; Stroud et al., 2013; Woodward et al., 2002). An example of this type of regional outreach program is the New Hampshire Perinatal Program, which has been in existence for over 30 years and routinely provides educational opportunities and an on-site review of all shared patients at least yearly with all referring facilities (Frank et al., 1999).

TRANSPORT TEAM COMPOSITION

Many different transport team compositions have been described, and ultimately the team composition should be appropriate for the type of care the neonate requires (Cornette, 2004a; Colyer, Sorensen, Wiggins, & Struwe, 2018; Davies, Bickell, & Tibby, 2010; Fenton et al., 2004; Fenton & Leslie, 2009; Insoft & Schwartz, 2015; Karlsen et al., 2011; Lee et al., 2002; Leppälä, 2010; Leslie & Stephenson, 2003; Lupton & Pendray; 2004; NANN, 2010; Stroud et al., 2013). A national survey by Karlsen et al. (2011) identified 26 different types of neonatal transport team compositions. There were 335 respondents to this survey, and only one team did not include either a neonatal nurse practitioner (NNP) or RN on the neonatal transport team. A recent study by Colyer et al. (2018) has suggested that an RN/paramedic team may present an additional type of configuration for a neonatal specialty transport team.

The role of the NNP has been compared with the pediatric house-staff as a member of the transport team (Cornette, 2004a, 2004b; Fenton et al., 2004; Fenton & Leslie, 2009; Leslie & Stephenson, 2003). There is ample evidence that the care provided by NNPs is at least comparable and potentially improved due to the consistency and experience this role brings to the transport process. In addition, it is less and less frequent that pediatric house-staff are involved in neonatal transports, mainly due to restrictions on duty hours and limited clinical time spent in neonatal units. Because of these constraints, it is now generally recommended that pediatric house-staff not be part of the transport team unless they receive additional training (Fenton & Leslie, 2009; Woodward et al., 2002).

Lee et al. (2002) analyzed three different compositions of transport teams: an EMT, an RN team, or a combined team of RN and RT. An MD would accompany any of these teams if the condition of the neonate warranted that level of care; however, the analysis did not show that the presence of a physician affected the outcome of the transport. The patient outcomes of the three types of teams were not significantly different. A cost analysis was performed and the RN team was found to be the most cost-effective model for most transports, followed by the combined team, and then the EMT team.

The survey by Karlsen et al. (2011) classified the transport team as being either unit-based or dedicated. The two most common unit-based team compositions in this survey were RN–RT or RN–RT–NNP. The unit-based teams were staffed by neonatal intensive care personnel, who were responsible for patient care when not on transport, similar to the RN team and combined team in the cost analysis by Lee et al. (2002). Unit-based teams generally performed fewer than 200 transports per year.

Dedicated teams in this survey were most commonly composed of RN–RT or RN–RN. The dedicated teams usually had a volume of over 200 neonatal transports per year and covered a geographical distance of greater than 100 miles. Only about 37% of these teams transported neonates exclusively; 50% of the dedicated teams were combined neonatal–pediatric teams.

Fenton and Leslie (2009) have suggested that the professional background of the transport team members is less important than the training each member of the team receives in terms of providing excellent patient care, performing procedural skills, communicating with the family and referring facility providers, and being part of the quality assurance process of the regional transport system. The AAP Section of Transport Medicine (Insoft & Schwartz, 2015) and NANN (2010) have developed guidelines for the interprofessional training of the neonatal transport team. The composition of the transport team should always be appropriate for the level of care the neonate will require in order to ensure a safe, effective, and efficient transfer to the tertiary or quaternary facility (Stroud et al., 2013).

TRANSPORT TEAM TRAINING

The neonatal transport team must possess the skills to provide care at both the referring facility and in a mobile environment (Insoft & Schwartz, 2015). Team configuration may vary depending upon the anticipated needs of the neonate. Each team member should have defined roles and responsibilities, but an understanding of other team members' roles is essential (Insoft & Schwartz, 2015). The educational process for members of the transport team should include didactic lectures, observation of the transport process, and clinical training including procedures with defined metrics for ensuring competencies. In addition, the importance of effective and efficient communication must be a part of the education curriculum. Neonatal transports are generally a low-volume, high-risk endeavor and the use of simulation training is becoming increasingly commonplace in team training (Campbell & Dadiz, 2016; Insoft & Schwartz, 2015; LeFlore & Anderson, 2008; Stroud et al., 2013). Quality and safety metrics also need to be incorporated—and in some cases developed—in transport team training, as well as in ongoing assessment of the team. Some potential metrics include adverse events on transport, medication errors, mobilization time, pain assessments, procedural skills such as intubation and umbilical catheter placement, thermoregulation, and use of "lights and sirens" during the transport (Bigham & Schwartz, 2013; Campbell & Dadiz, 2016; Colyer et al., 2018; Davidson, Utarnachitt, Mason, & Sawyer, 2018; Duby et al., 2018; Insoft & Schwartz, 2015; McLean, Gothard, Parrish, & Bigham, 2017; Reichert, Gothard, Schwartz, & Bigham, 2016; Stroud et al., 2013).

MODE OF TRANSPORTATION

Neonatal transports generally occur by ambulance, fixed wing aircraft, helicopter, or boat (Insoft & Schwartz, 2015; Karlsen et al., 2011; Leppälä, 2010; Lupton & Pendray, 2004; NANN, 2010). The first recorded helicopter transport in the United States occurred in 1967 in Illinois (Perry, 2017). Other modes of transportation have been reported, including walking or riding in a rickshaw (Mori et al., 2007). If more than one mode of transportation is available, the decision should be based upon the condition of the neonate and the distance to the tertiary facility. To ensure the safety of the transport team and neonate, weather conditions may also need to be taken into account.

In the survey by Karlsen et al. (2011) the majority of transports were by ground. Generally speaking, for shorter distances ground transport is the preferable mode. For distances that will require 2 hours or more of travel time one way, air transport may be more appropriate (Karagol, Zenciroglu, Ipek, Kundak, & Okumus, 2011; Lupton & Pendray, 2004). Transport by helicopter is the most expensive and ambulance the least expensive (Insoft & Schwartz, 2015; Lupton & Pendray, 2004; Wright, 2000). Whatever mode of transportation is used, the team must be oriented to and comfortable with the configuration and equipment of the ground or air ambulance.

STABILIZATION BY THE TRANSPORT TEAM

Once the transport team has arrived at the referring facility, they should introduce themselves and receive a hand-off from the local team. This hand-off is critical, as it will inform the transport team about care already received, prevent unnecessary duplication of care, and help guide the next steps (Wright, 2000). A successful hand-off will help expedite transporting the neonate to the tertiary facility safely. Exhibit IV.1 provides an example of information to be included in the hand-off to the transport team.

Once the hand-off is accomplished, the transport team should assess the neonate, continue with the stabilization, and provide any additional care to ensure a safe and efficient transfer to the tertiary center. It is crucial that prior to transport, the neonate has a stable airway, receives any cardiovascular support needed, vascular access is ensured if necessary, and appropriate medications have been provided. Continued close attention should also be paid to thermoregulation and glucose homeostasis (Cornette, 2004b; Fenton et al., 2004; Leslie & Stephenson, 2003). The neonate should also have pain assessments performed and documented during the transport process (Reichert et al., 2016). Special consideration should be paid to ensuring that all tubes and catheters are in good position and secure; an accidental extubation or dislodgement of an umbilical line could result in destabilizing an already fragile neonate (McLean et al., 2017).

Additional transport therapies that may be unique to the neonatal population include whole-body cooling for infants with concern for hypoxic ischemic encephalopathy or phototherapy for infants nearing exchange transfusion criteria for hyperbilirubinemia (Banda, 2016; Bellini & Risso, 2016; Bourque et al., 2018; Chaudhary, Farrer, Broster, McRitchie, & Austin, 2013; Waterham et al., 2015). These therapies may require the transport team to bring additional equipment such as cooling packs or mattresses for active whole-body cooling or a bilirubin blanket.

Communication by the transport team back to the tertiary center is an essential part of the stabilization and transport process (Harbour & Oddi, 2016; Wilson, Kochar, Whyte-Lewis, Whyte, & Lee, 2017). The Joint Commission (2017) recommends the use of standardized tools and methods to improve communication and hand-offs. A quality improvement project by Wilson et al. (2017) used the SBAR tool (Situation, Background, Assessment, Recommendation) to improve communication between the transport team and the medical control officer.

TRANSPORT EQUIPMENT

The transport equipment allows the neonatal transport team to bring many aspects of the tertiary unit to the referring facility. The team members need to be comfortable using all the equipment and as much as possible it should be standardized in terms of location, type, and so forth. When choosing transport equipment, there are

EXHIBIT IV.1

SAMPLE HAND-OFF FORM

Referring hospital_____ Referring provider_____

Infant Data

Name_____ Date of birth_____

Gestational age_____ Birth weight_____

Reason for transport_____

_____

Delivery method_____

Reason for delivery_____

Apgar score 1 min_____ 5 min_____ 10 min_____

Resuscitation included_____

_____

Maternal Data

Name_____ Date of birth _____

Gravida _____ Para _____Term_____ Ab _____ Preterm _____ Living_____

Prenatal Labs

Blood group _____ Antibody_____

Rubella _____ HBsAg _____ HIV_____ Syphilis _____ GBS _____

GC_____ Chlamydia_____ CF screen _____

Other _____

Pregnancy complications _____

_____

Other Pertinent Information

Dad's name _____ Date of birth _____

_____

_____

Interventions by Referring Team

Procedures

____Intubation Size ETT_____ Insertion marking_____

____UAC Size catheter____ Insertion marking_____

____UVC Size catheter____ Insertion marking_____

____PIV Size catheter____ Insertion site_____

____Chest tube Size catheter____ Insertion site_____

____CXR Results:_____

Ventilator Settings: PIP_____ PEEP_____ Rate_____ FiO_2_____

Vital Signs: HR_____ RR_____ BP_____ Temp_____ O_2 sat_____

(*continued*)

EXHIBIT IV.1 (*continued*)

Lab Work

Blood gases_____

_____

_____

CBC _____

Blood culture _____

Other culture _____

Type and screen _____

Medications

Name_____ Dose_____ Time given_____

Name_____ Dose_____ Time given_____

Name_____ Dose_____ Time given_____

Name_____ Dose_____ Time given_____

Box IV.2

TRANSPORT BAG EQUIPMENT

Medications

- Antibiotics
- Anticonvulsants
- Code medications
- Inotropic agents
- Intravenous solutions
  - Dextrose 5% and 10%
  - Normal saline
- Prostaglandins
- Intubation premedications
- Surfactant

Respiratory Equipment

- Endotracheal tubes
- End-tidal carbon monoxide monitoring
- Laryngoscope and blades
- Resuscitation bag and masks
- Laryngeal mask airways
- Continuous positive airway pressure prongs
- Portable blood gas analyzer

Additional Equipment

- Monitoring
  - ECG leads
  - O_2 saturation probes
  - Transducer
  - Temperature probes

(*continued*)

Box IV.2 (*continued*)

- Procedural
  - Umbilical catheter insertion
  - Chest tube insertion
- Vascular access
  - IV catheters
  - Intra-osseous needles
- Miscellaneous
  - Decompression tubes
  - Equipment for sterile procedures
    - Gown, mask, gloves, provodone-iodine, chlorhexidine, alcohol
  - Point of care glucose monitoring
  - Suction catheters
  - Tube and catheter stabilizing equipment
  - Reference manuals

several important considerations. Safety should be an overriding concept and all equipment should meet all federal, state, and local regulations. The equipment should have the ability to run by both electricity and battery power. It will need to withstand changes in temperature and, if air transport is used, changes in altitude.

The transport isolette is the primary tool used by the neonatal transport team. It needs to be able to safely transport and keep warm a neonate weighing less than 1 kg up to 5 to 6 kg. The neonate should be visible and easily accessible to the team throughout the transport. The transport isolette should have additional equipment mounted to it including a cardiorespiratory monitor, IV pumps, air and oxygen tanks, oxygen blender for appropriate O_2 delivery, and a transport ventilator. There should also be space to add additional equipment if necessary, such as inhaled nitric oxide (Cornette, 2004b; Fenton et al., 2004; Insoft & Schwartz, 2015; Leppälä, 2010; Lupton & Pendray, 2004; Lutman & Petros, 2008; NANN, 2010).

In addition to the isolette and mounted equipment, the transport team will need to bring other smaller, but equally important items that are usually kept ready to go in transport bags. This will allow the team to perform procedures and stabilize the neonate with equipment that is familiar to them. Each transport program should decide upon the specific items to be brought; Box IV.2 lists common equipment to be found in transport bags.

DOCUMENTATION

The regional transport service should have the ability to document all transport calls and advice given to the referring center. There should also be documentation regarding the time of phone calls and dispatch of the transport team. Leslie and Fenton (2012) have suggested that individual transports be defined as planned, unplanned, or time-critical. If a transport is designated as time-critical, the transport team should be able to be mobilized in 30 minutes or less.

The referring facility should provide the transport team with copies of the neonate's medical record that includes a delivery summary, initial presentation, and summary of the stabilization process, including laboratory values. A copy of the maternal history, including pertinent prenatal information, should also be included. Hard copies or CDs of x-rays or other imaging studies should also be available to the transport team (Cornette, 2004b; Das & Leuthner, 2004; Leppälä, 2010).

Prior to the departure of the transport team, it is imperative that consent forms authorizing the transport be obtained and signed. There should be documentation of consent from the parents to transport their infant to the tertiary center. There may also be state, local, or third-party consent forms that need to be signed by the referring provider and a member of the transport team who is receiving care of the neonate (Cornette, 2004b; Lupton & Pendray, 2004).

Documentation by the neonatal transport team should include a flow sheet for vital signs, respiratory status, intake and output, and a brief description of interventions provided. A full note by the transport team leader describing the transport should be entered into the neonate's chart at the tertiary center. This note should include the time of arrival at the referring facility, time of arrival at the tertiary center, mode of transportation, and care given during the transport, both at the referring facility and enroute. It is recommended that a copy of this note be sent to the referring provider as well as the neonate's primary care provider.

FAMILY-CENTERED CARE DURING TRANSPORT

The transport of a critically ill neonate is particularly stressful for parents who may or may not have anticipated the birth of an ill neonate and may not be able to immediately go to the receiving facility to fully participate in the care of their infant (Buchanan, 2009; Das & Leuthner, 2004; Dulkerian et al., 2011; Duritza, 2009; Franklin, 2006; Hawthorne & Killen, 2006; Hogan & Logan, 2004; Leppälä, 2010; Macnab et al., 1999; Mullaney et al., 2014; Steeper, 2002; Wilman, 1997). It has been suggested that early parental participation in the care of their infant helps to foster the parent–infant relationship. Parental separation from their infant, which is inherent in the transport process, can adversely impact the successful development of this relationship (Franklin, 2006; Obeidat, Bond, & Callister, 2009). The neonatal transport team needs to be cognizant of this and try to facilitate parental involvement in the care of their infant during the transport process.

The first way parents participate in the care of their infant is by information sharing. Steeper (2002) has noted that there is a lack of information about how parents perceive the communication they receive about their infant during the transport process. Until more definitive information is available, the transport team should use the guidance of communication strategies already identified for parents whose infants are in the NICU (Howland, 2007; Saunders, Abraham, Crosby, Thomas, & Edwards, 2003; Sharp, Strauss, & Lorch, 1992). This communication should begin when the local team identifies the need for transport. The parents should be informed of the reason the neonate needs to be transported for a higher level of care, the name of the facility he/she is going to, when the transport team is expected to arrive, the mode of transportation, and if it is possible for the mother to be transferred to the tertiary facility or if she can be discharged to travel to the receiving facility (Das & Leuthner, 2004; Leppälä, 2010; NANN, 2010; Wright, 2000).

For the parents and family of an ill neonate, their first experience with the neonatal intensive care team will be the transport team. Most neonatal units pride themselves on providing family-centered care, realizing that the parents and family are not visitors to the neonatal unit, but a part of the team caring for the ill neonate. If this is truly believed, family participation in the care of their infant needs to begin during the transport process. Once the transport team arrives, they need to continue to keep parents informed as the local team has. The transport team needs to introduce themselves, and parents should be given the opportunity to stay with their infant during the stabilization by the transport team (NANN, 2010). Parents should be told what the assessments of the transport team are, any additional procedures to be done in the referring facility or that may be necessary during the transport process, and be given the opportunity to ask questions. If the parents have not been able to be present while readying the neonate for transport, the team should go to the mother's room so that they can see and touch their infant prior to leaving the referring facility.

Many transport teams also provide the parents with some written information about the NICU the neonate is going to that includes the phone number to the unit as well as a map for the parents to use. The team should ensure that the parents have a photograph of their infant; if not, the team should have the ability to provide one. Parents will also need information about the anticipated duration of the transport, and if they will not be accompanying the baby, they should receive a phone call from the transport team once the infant has safely arrived in the NICU.

SUMMARY

The transport of an ill neonate from a Level I or Level II facility will always be a stressful and challenging experience. The transport process begins with the identification of the ill neonate, transitions through the transport team, and ends with admission to the NICU. A well-developed regional neonatal or perinatal program helps to ensure the smooth transition of the neonate from the referring to the receiving facility. The goal of the neonatal transport team, a part of the regional program, is to provide high-quality, safe, efficient, and family-centered care to the ill neonate prior to arrival at the tertiary unit.

REFERENCES

Banda, D. (2016). Transport of neonates with severe jaundice on phototherapy: Implications for regional areas. *Journal of Paediatrics and Child Health*, *52*, 785. doi:10.1111/jpc.13196

Barfield, W. D., Papile, L.-A., Baley, J. E., Benitz, W., Cummings, J., Carlo, W. A., . . . Watterberg, K. L. (2012). Policy statement:

Levels of neonatal care. *Pediatrics, 130*(3), 587–597. doi:10.1542/peds.2012-1999

Bellini, C., & Risso, F. M. (2016). Phototherapy in transport for neonates with unconjugated hyperbilirubinemia. *Journal of Paediatrics and Child Health, 52*, 356. doi:10.1111/jpc.13130

Bigham, M. T., & Schwartz, H. P. (2013). Quality metrics in neonatal and pediatric critical care transport: A consensus statement. *Quality and Safety, 14*(5), 518–524. doi:10.1097/PCC.0b013e31828a7fc1

Bouchut, J.-C., Van Lancker, E., Chritin, V., & Gueugniaud, P.-Y. (2011). Physical stressors during neonatal transport: Helicopter compared with ground ambulance. *Air Medical Journal, 30*(3), 134–139. doi:10.1016/j.amj.2010.11.001

Bourque, S. L., Meier, S. A., Palmer, C., Melara, D. L., Grover, T. R., & Delaney, C. A. (2018). A quality initiative for optimal therapeutic hypothermia during transport for neonates with neonatal encephalopathy. *Pediatric Quality and Safety, 2*(3), 1–7. doi:10.1097/pq9.0000000000000056

Buchanan, K. (2009). Failed neonatal transport. *Advances in Neonatal Care, 9*(2), 82–84. doi:10.1097/ANC.0b013e31819d4e6d

Campbell, D. M., & Dadiz, R. (2016). Simulation in neonatal transport medicine. *Seminars in Perinatology, 40*, 430–437. doi:10.1053/j.semperi.2016.08.003

Chang, A. S. M., Berry, A., Jones, L. J., & Sivasangari, S. (2015). Specialist teams for neonatal transport to neonatal intensive care units for prevention of morbidity and mortality (Review). *Cochrane Database of Systematic Reviews*, (10), CD007485. doi:10.1002/14651858.CD007485.pub2

Chaudhary, R., Farrer, K., Broster, S., McRitchie, L., & Austin, R. (2013). Active versus passive cooling during neonatal transport. *Pediatrics, 132*(5), 841–846. doi:10.1542/peds.2013-1686

Colyer, E., Sorensen, M., Wiggins, S., & Struwe, L. (2018). The effect of team configuration on the incidence of adverse events in pediatric critical care transport. *Air Medical Journal, 37*, 186–198. doi:10.1016/j.amj.2018.02.006

Cornette, L. (2004a). Contemporary neonatal transport: Problems and solutions. *Archives of Diseases of Children Fetal Neonatal Edition, 89*, F212–F214. doi:10.1136/adc.2003.046201

Cornette, L. (2004b). Transporting the sick neonate. *Current Paediatrics, 14*, 20–25. doi:10.1016/j.cupe.2003.09.001

Das, U. G., & Leuthner, S. R. (2004). Preparing the neonate for transport. *Pediatric Clinics of North America, 51*, 581–598. doi:10.1016/j.pcl.2004.01.002

Davidson, L. A., Utarnachitt, R. B., Mason, A., & Sawyer, T. (2018). Development and testing of a neonatal intubation checklist for an air medical transport team. *Air Medical Journal, 37*, 41–45. doi:10.1016/j.amj.2017.09.010

Davies, J., Bickell, F., & Tibby, S. M. (2010). Attitudes of paediatric intensive care nurses to development of a nurse practitioner role for critical care transport. *Journal of Advanced Nursing, 67*(2), 317–326. doi:10.1111/j.1365-2648.2010.05454.x

Duby, R., Hansen, M., Meckler, G., Skarica, B., Lambert, W., & Guise, J.-M. (2018). Safety events in high risk prehospital neonatal call. *Prehospital Emergency Care, 22*(1), 34–40. doi:10.1080/10903127.2017.1347222

Dulkerian, S. J., Douglas, W. P., & Taylor, R. M. (2011). Redirecting treatment during neonatal transport. *Journal of Perinatal and Neonatal Nursing, 25*(2), 111–114. doi:10.1097/JPN.0b013e31821a20ab

Duritza, K. (2009). Neonatal transport—A family support module. *Newborn and Infant Nursing Reviews, 9*(4), 212–218. doi:10.1053/j.nainr.2009.09.006

Fenton, A. C., & Leslie, A. (2009). Who should staff neonatal transport teams? *Early Human Development, 85*, 487–490. doi:10.1016/j.earlhumdev.2009.05.006

Fenton, A. C., Leslie, A., & Skeoch, C. H. (2004). Optimising neonatal transfer. *Archives of Diseases of Children Fetal Neonatal Edition, 89*, F215–F219. doi:10.1136/adc.2003.019711

Frank, J. E., Rhodes, T. T., Edwards, W. E., Darnall, R. A., Smith, B. D., Little, G. A., . . . Flanagan, V. A. (1999). The New Hampshire perinatal program: Twenty years of perinatal outreach education. *Journal of Perinatology, 19*(1), 3–8. doi:10.1038/sj.jp.7200129

Franklin, C. (2006). The neonatal nurse's role in parental attachment in the NICU. *Critical Care Nursing Quarterly, 29*(1), 81–85. doi:10.1097/00002727-200601000-00009

Harbour, D., & Oddi, M. (2016). Improving standardized hand-off communication through education for a pediatric neonatal critical care transport team. *Air Medical Journal, 35*, 283–284. doi:10.1016/j.amj.2016.07.020

Hawthorne, J., & Killen, M. (2006). Transferring babies between units: Issues for parents. *Infant, 2*(2), 44–46. Retrieved from http://www.infantjournal.co.uk/pdf/inf_008_pts.pdf

Healthy People 2030. (2019). Retrieved from https://www.healthypeople.gov/2020/topics-objectives/objective/mich-33

Hogan, D. L., & Logan, J. (2004). The Ottawa model of research use: A guide to clinical innovation in the NICU. *Clinical Nurse Specialist, 18*(5), 255–261. doi:10.1097/00002800-200409000-00010

Howland, L. C. (2007). Preterm birth: Implications for family stress and coping. *Newborn and Infant Nursing Reviews, 7*(1), 14–19. doi:10.1053/j.nainr.2006.12.008

Insoft, R. M., & Schwartz, H. P. (Eds.). (2015). *Guidelines for air and ground transport of neonatal and pediatric patients* (4th ed.). Elk Grove Village, IL: American Academy of Pediatrics.

The Joint Commission. (2017). *Sentinel event alert 58: Inadequate hand-off communication.* Retrieved from https://www.jointcommission.org/sentinel_event_alert_58_inadequate_handoff_communications/

Karagol, B. S., Zenciroglu, A., Ipek, M. S., Kundak, A. A., & Okumus, N. (2011). Impact of land-based neonatal transport on outcomes in transient tachypnea of the newborn. *American Journal of Perinatology, 28*(4), 331–336. doi:10.1055/s-0030-1270115

Karlsen, K. A. (2017). The S.T.A.B.L.E. program. Retrieved from http://www.stableprogram.org

Karlsen, K. A., Trautman, M., Price-Douglas, W., & Smith, S. (2011). National survey of neonatal transport teams in the United States. *Pediatrics, 128*, 685–691. doi:10.1542/peds.2010-3796

Kilpatrick, S. J., Papile, L.-A., & Macones, G. A. (Eds.). (2017). *Guidelines for perinatal care* (8th ed.). Elk Grove Village, IL: American Academy of Pediatrics.

Lee, S. K., Zupancic, J. A. F., Sale, J., Pendray, M., Whyte, R., Brabyn, D., ... Whyte, H. (2002). Cost-effectiveness and choice of infant transport systems. *Medical Care, 40*(8), 705–716. doi:10.1097/01.MLR.0000020930.04786.F9

LeFlore, J. L. L., & Anderson, M. (2008). Effectiveness of 2 methods to teach and evaluate new content to neonatal transport personnel using high-fidelity simulation. *Journal of Perinatal Neonatal Nursing, 22*(4), 319–328. doi:10.1097/01.JPN.0000341364.60693.70

Leppälä, K. (2010). Whether near or far . . . transporting the neonate. *Journal of Perinatal and Neonatal Nursing, 24*(2), 167–171. doi:10.1097/JPN.0b013e3181db5341

Leslie, A., & Fenton, A. (2012). Categorising neonatal transports. *Archives of Diseases of Children Fetal Neonatal Edition, 97*(1), F77. doi:10.1136/archdischild-2011-300509

Leslie, A., & Stephenson, T. (2003). Neonatal transfers by advanced neonatal nurse practitioners and paediatric registrars. *Archives of Diseases of Children Fetal Neonatal Edition, 88*, F509–F512. doi:10.1136/fn.88.6.F509

Little, G. A., Horbar, J. D., Wachtel, J. S., Gluck, P. A., & Muri, J. H. (2010). Evolution of quality improvement in perinatal care. In Committee on Perinatal Health (Ed.), *Toward improving the outcome of pregnancy III* (pp. 9–18). White Plains, NY: March of Dimes.

Lupton, B. A., & Pendray, M. R. (2004). Regionalized neonatal emergency transport. *Seminars in Neonatology, 9*, 125–133. doi:10.1016/j.siny.2003.08.007

Lutman, D., & Petros, A. (2008). Inhaled nitric oxide in neonatal and paediatric transport. *Early Human Development, 84*, 725–729. doi:10.1016/j.earlhumdev.2008.08.003

Macnab, A. J., Richards, J., & Green, G. (1999). Family-oriented care during pediatric inter-hospital transport. *Patient Education and Counseling, 36*, 247–257. doi:10.1016/S0738-3991(98)00090-1

McLean, J., Gothard, D. D., Parrish, P. R., & Bigham, M. T. (2017). Mobilization time among neonatal/pediatric transport teams: The ground and air medical quality in transport (GAMUT) collaborative. *Air Medical Journal, 36*, 209. doi:10.1016/j.amj.2017.04.010

McNamara, P. J., Mak, W., & Whyte, H. E. (2005). Dedicated neonatal retrieval teams improve delivery room resuscitation of outborn premature infants. *Journal of Perinatology, 25*, 309–314. doi:10.1038/sj.jp.7211263

Messner, H. (2011). Neonatal transport: A review of the current evidence. *Early Human Development, 87*(Suppl.), S77. doi:10.1016/j.earlhumdev.2011.01.018

Mori, R., Fujimaura, M., Shiraishi, J., Evans, B., Corkett, M., Negishi, H., & Doyle, P. (2007). Duration of inter-facility neonatal transport and neonatal mortality: Systematic review and cohort study. *Pediatrics International, 49*, 452–458. doi:10.1111/j.1442-200X.2007.02393.x

Mullaney, D. M., Edwards, W. H., & DeGrazia, M. (2014). Family-centered care during acute neonatal transport. *Advances in Neonatal Care, 14*(5S), S16–S23. doi:10.1097/ANC.0000000000000119

National Association of Neonatal Nurses. (2010). *Neonatal nursing transport standards: Guidelines for practice* (3rd ed.). Glenview, IL: Author.

Obeidat, H. M., Bond, E. A., & Callister, L. C. (2009). The parental experience of having an infant in the newborn intensive care unit. *The Journal of Perinatal Education, 18*(3), 23–29. doi:10.1624/105812409X461199

Perry, S. E. (2017). A historical perspective on the transport of premature infants. *Journal of Obstetrics, Gynecologic and Neonatal Nursing, 46*, 647–656. doi:10.1016/j.jogn.2016.09.007

Reichert, R. J., Gothard, M. D., Schwartz, H. P., & Bigham, M. T. (2016). Benchmarking pain assessment rate in critical care transport. *Air Medical Journal, 35*, 344–347. doi:10.1016/j.amj.2016.07.001

Robles, D., Blumenfeld, Y. J., Lee, H. C., Gould, J. B., Main, E., Profit, J., . . . Druzin, M. (2017). Opportunities for maternal transport for delivery of very low birth weight infants. *Journal of Perinatology, 37*, 32–35. doi:10.1038/jp.2016.174

Rochefort, C. M., & Lamothe, L. (2011). Forcing the system: A configuration analysis of a regional neonatal-perinatal health network. *Health Care Management Review, 36*(3), 241–251. doi:10.1097/HMR.0b013e3182104e34

Saunders, R. P., Abraham, M. R., Crosby, M., Thomas, K., & Edwards, W. E. (2003). Evaluation and development of potentially better practices for improving family-centered care in neonatal intensive care units. *Pediatrics, 111*(Suppl. E1), e437–e449. Retrieved from https://pediatrics.aappublications.org/content/111/Supplement_E1/e437

Sharp, M. C., Strauss, R. P., & Lorch, S. C. (1992). Communicating medical bad news: Parent's experiences and preferences. *Journal of Pediatrics, 121*, 539–546. doi:10.1016/S0022-3476(05)81141-2

Sinkin, R. A., & Chisholm, C. A. (Eds.). (2016). *Perinatal Continuing Education Program (PCEP)* (3rd ed.). Elk Grove Village, IL: American Academy of Pediatrics.

Staebler, S. (2011). Regionalized systems of perinatal care: Health policy considerations. *Advances in Neonatal Care, 11*(1), 37–42. doi:10.1097/ANC.0b013e318206fd5a

Steeper, S. (2002). Neonatal transportation: Exploring parental views. *Journal of Neonatal Nursing, 8*(6), 173–176.

Stroud, M. H., Trautman, M. S., Meyer, K., Moss, M. M., Schwartz, H. P., Bigham, M. T., . . . Insoft, R. (2013). Pediatric and neonatal interfacility transport: Results from a national consensus conference. *Pediatrics, 132*(2), 359–366. doi:10.1542/peds.2013-0529

Warner, B., Altimier, L., & Imhoff, S. (2002). Clinical excellence for high risk neonates: Improved perinatal regionalization through coordinated maternal and neonatal transport. *Neonatal Intensive Care, 15*(6), 33–38.

Waterham, M., Bhatia, R., Donath, S., Molesworth, C., Tan, K., & Stewart, M. (2016). Phototherapy in transport for neonates with unconjugated hyperbilirubinemia. *Journal of Paediatrics and Child Health, 52*, 67–71. doi:10.1111/jpc.12984

Wilman, D. (1997). Neonatal transport: The effect on parents. *Journal of Neonatal Nursing, 3*(5), 16–22.

Wilson, E., Kochar, A., Whyte-Lewis, A., Whyte, H., & Lee, K.-S. (2017). Evaluation of situation, background, assessment, recommendation tool during neonatal and pediatric interfacility transport. *Air Medical Journal, 36*, 182–187. doi:10.1016/j.amj.2017.02.013

Woodward, G. A., Insoft, R. M., Pearson-Shaver, A. L., Jaimovich, D., Orr, R. A., Chambliss, R., . . . Westergaard, F. (2002). The state of pediatric interfacility transport: Consensus of the second National Pediatric and Neonatal Interfacility Transport Medicine Leadership Conference. *Pediatric Emergency Care, 18*(1), 38–43. doi:10.1097/00006565-200202000-00013

Wright, J. D. (2000). Before the transport team arrives: Neonatal stabilization. *The Journal of Perinatal and Neonatal Nursing, 13*(4), 87–107. doi:10.1097/00005237-200003000-00007

V

Introduction to Vascular Access

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INTRODUCTION

As the threshold of viability continues to recede, the challenge of nourishing the premature survivors has grown. Premature infants and medically and surgically complex term infants require optimal amounts of protein, carbohydrates, and fats to achieve growth, and the method of delivering these nutrients is crucial to their safe delivery. Current traditionally utilized vascular access devices for neonates include umbilical catheters, peripherally inserted central catheters (PICCs), central venous catheters, midline catheters, and peripheral intravenous (PIV) devices, with the addition of recently available extended dwell peripheral intravenous catheters (EPIV; see Table V.1).

The process of selection of the device should consider the individual patient's needs and results following a risks versus benefits analysis. These considerations include the chemical properties of the therapy such as osmolarity, pH, and irritant or vesicant properties, specific patient needs, and the intended duration of therapy. The Centers for Disease Control and Prevention (CDC) recommends using "a midline catheter or peripherally inserted central catheter (PICC), instead of a short peripheral catheter, when the duration of IV therapy will likely exceed six days" (O'Grady et al., 2011, p. 26). Early standards of practice provided for medications with a pH of less than 5 or greater than 9 as a sole factor, indicating the need for central venous access (Infusion Nurses Society [INS], 2011). Current decision making for the type of intravenous or central venous access should be based on multiple factors including anticipated duration of therapy, vesicant properties and number of infusates, patient conditions, and osmolarity greater than 600 mOsm/L (Gorski, Hagle, & Bierman, 2015).

The most commonly used first-line intravenous device is the peripheral intravenous device (PIV). These are often inserted in the veins in the hands and feet with distal to proximal progression should repeated PIVs be required. PIVs are used for nonirritant solutions or medications with dextrose concentrations of 12.5% or less (Alexander, Corrigan, Gorski, Hankins, & Perucca, 2010).

Umbilical arterial catheters (UACs) may be placed initially when frequent blood sampling and monitoring is indicated. The UAC catheter tip should be located between T6 and T9 for high position and L3 and L4 for low position (Said & Rais-Bahrami, 2013a). It is recommended to limit UAC duration to no more than 5 days (O'Grady et al., 2011).

Umbilical venous catheters (UVCs) may be placed initially for infusion of total parenteral nutrition, medications, and blood administration. The UVC catheter tip should be located in the inferior vena cava near the junction with the right atrium (Said & Rais-Bahrami, 2013b). It is recommended to limit UVC duration to 7 days to minimize risk of central line–associated bloodstream infection (Butler-O'Hara, D'Angio, Hoey, & Stevens, 2012).

Midline catheters can be utilized for infusion of medications and fluids with osmolarity less than 900 mOsm/L (Gorski et al., 2016). The midline catheter can be placed in basilic, cephalic, or median cubital position with the catheter tip maintained below the axilla. In infants, a midline catheter can also be placed in the lower extremity veins with the catheter tip maintained below the groin and in scalp veins with the catheter tip maintained in the jugular vein above the clavicle (Gorski et al., 2016). Midline catheters can remain in place as patient needs require and there are no signs of complications. Midline catheters are utilized for nonirritant solutions or medications with dextrose concentrations of 12.5% or less.

Recently available EPIV catheters are being inserted in similar locations to midline catheters and are used for nonirritant solutions or medications with dextrose concentrations of 12.5% or less (Chenoweth, Guo, & Chan, 2018).

PICCs are now commonly used to administer total parenteral nutrition and hyperosmolar medications in neonatal intensive care. When properly maintained, PICCs provide reliable long-term access for delivery of parenteral nutrition and hyperosmolar or irritant medications, fewer interruptions in therapy, decreased incidence of painful procedures and stress to infants, and fewer opportunities for needlestick exposure to healthcare providers. The disadvantages include: the need for radiographic confirmation of catheter tip location with insertion and following repositioning, specialized training required, risk for extravasation, phlebitis, pericardial and pleural effusion, occlusion, thrombosis, infection, and migration or dislodgement (see Table V.2).

The key indications for a PICC are the anticipated need for long-term parenteral nutrition or hyperosmolar medications. Typical patient profiles are extreme prematurity, diagnoses with delayed feedings, patients with congenital anomalies limiting vascular options, and those requiring long-term vascular access for nutrition or treatment. The most commonly used veins for PICC placement are the basilic, cephalic, greater and lesser saphenous,

TABLE V.1

TYPES OF INTRAVENOUS DEVICES

Type of Device	Intended Duration	Average Dwell Time	Type of Infusion	Optimal Tip Location
Peripheral intravenous	Short term	47 hours (Legemaat et al., 2016; Leick-Rude & Haney, 2006)	Nonirritant, isotonic solutions D12.5% or less (Pettit, 2003)	Peripheral
Midline	5–7 days	8.7 days to as many as 80 days (Leick-Rude & Haney, 2006; Wyckoff, 1999)	Nonirritant, isotonic solutions D12.5% or less	Upper portion of extremity, below axilla, above clavicle, away from areas of flexion
Extended dwell peripheral intravenous	Up to 29 days	4 days ± 2.3 days (Chenoweth et al., 2018)	Nonirritant, isotonic solutions D12.5% or less	Below the shoulder
Peripherally inserted central catheters	More than 6 days to long term	17 days to indefinitely as needed (Goldwasser, Baia, Kim, Taragin, & Angert, 2017)	Parenteral nutrition, vesicant therapy, infusates pH <5 or >9, >600 mOsm/L >D12.5%	Lower 1/3 of SVC or IVC above level of diaphragm
Percutaneous central venous catheter	5–7 days	5–7 days	Parenteral nutrition, vesicant therapy, infusates pH <5 or >9, >600 mOsm/L	Lower 1/3 of SVC or IVC above level of diaphragm

IVC, inferior vena cava; SVC, superior vena cava.

TABLE V.2

PREVENTION AND MANAGEMENT OF PICC COMPLICATIONS

Complication	Risk Factors	Prevention	Management
Central line–associated bloodstream infection	Prematurity Inexperienced or untrained caregivers Multiple manipulations of catheter Prolonged dwell time Contamination of catheter hub or needleless connector	Central line bundle elements including: Specially trained personnel Maximum sterile barrier precautions Maintaining an occlusive dressing Meticulous catheter care Hub hygiene Chlorhexidine or povidone iodine for skin antisepsis Limiting breaks in line Daily review of line necessity	Intravenous antibiotic therapy Removal of catheter if unable to clear infection or if gram-negative bacilli, *Staphylococcus aureus,* or *Candida* (Benjamin et al., 2001; Karadag-Oncel et al., 2015)
Occlusion	Low flow rates <0.5 mL/hours Inadequate flushing	Flushing before and after incompatible medications Maintaining adequate minimum infusion rates (0.5–2 mL/hours)	Clearing agents specific to etiology may be used Thrombolytics can be instilled according to manufacturer's directions
Phlebitis	Catheter tip outside the SVC or IVC Rapid or traumatic insertion Cephalic or saphenous vein insertion Catheter mobility due to inadequate securement	Use smallest size catheter that will accommodate therapy Screen infusates for irritant or vesicant properties, hyperosmolarity, or extreme pH (<5 or >9). Maintain secure occlusive dressing Position catheter tip in SVC or IVC Slow gentle insertion technique	Warm compresses over the vein every 4 hours and elevation of the extremity Often resolves spontaneously If it does not resolve or worsens after 24 hours, may need to discontinue the catheter

(*continued*)

TABLE V.2

PREVENTION AND MANAGEMENT OF PICC COMPLICATIONS (*continued*)

Complication	Risk Factors	Prevention	Management
Thrombosis	Catheter tip outside SVC or IVC Catheter mobility Left-sided insertion in upper extremity Protein C, protein S, or antithrombin deficiencies	Use smallest size catheter that will accommodate therapy Position catheter tip in SVC or IVC	Management and diagnostics include: Venogram Antithrombolytics Removal of catheter
Extravasation	Catheter tip outside SVC or IVC Irritant or hyperosmolar infusions	Evaluate infusion needs in device selection Position catheter tip in SVC or IVC for optimal hemodilution Frequent, at least hourly site assessment	Radiographic confirmation of catheter tip location Treat specific to area of extravasation Remove catheter
Pericardial/ pleural effusion	Catheter tip outside SVC or IVC Inadequate securement	Position catheter tip in SVC or IVC for optimal hemodilution Frequent, at least hourly site assessment Maintain secure dressing	Stop infusion Chest x-ray and echocardiogram for pericardial effusion Attempt to aspirate blood from catheter while awaiting imaging Withdraw catheter to proper position in SVC or IVC Repeat radiographic confirmation
Migration/ dislodgement	Loose or inadequate dressings Tension on tubing and catheter	Frequent, at least hourly site assessment Maintain secure dressing	Reevaluate catheter tip location Determine if catheter tip location is appropriate for therapy required Consider catheter exchange or alternate site if new tip location is not satisfactory

IVC, inferior vena cava; PICC, peripherally inserted central catheters; SVC, superior vena cava.

posterior auricular, and temporal. Other veins that may be utilized include the external jugular, axillary, femoral, and popliteal. As venous anatomy progresses from distal toward the head, the size of these vessels increases in diameter, creating optimal blood flow for hemodilution to minimize vessel damage. In the upper extremity, the basilic and cephalic veins flow directly into the axillary vein, then the subclavian vein, then the brachiocephalic vein into the superior vena cava (SVC). In the scalp, the posterior auricular and temporal veins flow directly into the jugular vein, then into the subclavian vein, the brachiocephalic, and the SVC. For catheters inserted into the veins of the upper extremity or scalp, the optimal catheter tip location is in the SVC (Food and Drug Administration, 1989; Gorski et al., 2016; Wyckoff & Sharpe, 2015). In the lower extremities, the greater and lesser saphenous veins flow directly into the femoral vein, then the iliac, then the inferior vena cava (IVC). For catheters inserted into the veins in the lower extremities, the optimal catheter tip location is in the IVC between the right atrium and diaphragm (Wyckoff & Sharpe, 2015). Radiographic confirmation should be obtained following catheter insertion and any adjustments to reposition the catheter, and if signs or symptoms suspicious for a complication are present.

Insertion Procedure

- Evaluate needs and duration of intended therapy.
- Discuss with family and obtain informed consent.
- Perform physical assessment for vein selection.
- Measure distance from intended insertion site along vein track to SVC for upper extremity or scalp vessels or IVC for lower extremity vessels.
- Gather insertion kit, catheter, introducer, sterile gloves, maximum sterile barriers, and other needed supplies.
- Prepare patient for procedure, including pharmacologic and developmental comfort measures.
- Don hair covering and mask.
- Perform hand hygiene.
- Prepare sterile field and equipment.
- Prepare catheter by flushing and trimming to premeasured length.
- Position patient as developmentally appropriate.
- Prepare insertion site by disinfecting skin with antimicrobial agent. Chlorhexidine gluconate or povidone iodine may be used. Chlorhexidine may be used with caution in premature infants or infants less than 2 months of age. These products may cause irritation or chemical burns.
- Utilize maximum sterile barrier precautions to isolate the extremity or insertion site.
- Apply sterile tourniquet.
- Insert introducer bevel up at 15° to 30° angle and observe for blood return. Once blood return is obtained, if using an over-the-needle sheath introducer, remove the needle.

- Remove tourniquet.
- Place catheter in introducer lumen using nontoothed or protected forceps and thread catheter in small increments to premeasured depth.
- Remove introducer per manufacturer's directions.
- Apply gentle pressure to site until bleeding stops.
- Verify inserted and externally lying catheter length.
- If a catheter with stylet is used, remove stylet at this time.
- Aspirate to confirm blood return and flush to confirm patency.
- Attach luer-lock extension tubing if not in catheter apparatus.
- Remove povidone iodine from skin and allow to dry.
- Secure catheter to skin and apply sterile transparent occlusive dressing.
- Obtain radiographic confirmation of catheter tip location in SVC or IVC.
- Reposition catheter if not in SVC or IVC.
- Obtain radiographic reconfirmation of catheter tip location if adjustments are made.
- Document procedure, any repositioning, radiographic confirmation, premedication, catheter specifics (including brand and lot number), trimmed length, inserted length, and patient tolerance.

Points for Practice in PICC Maintenance

- Be sure that the catheter tip location correlates with type of infusion.
- Infusions should be no greater than D12.5 if catheter tip location is not central in SVC or IVC.
- Secure and dress catheter to enable visualization of insertion site.
- Change dressing if it becomes loose, nonocclusive, moist, or soiled.
- Maintain adequate minimum infusion rates to prevent occlusion.
- Flush with no smaller than a 10 mL syringe per manufacturer's directions.
- If locking of catheter is desired, flush with minimal volumes of normal saline or heparin as specified in facility protocols (INS, 2008).

Assessment of the catheter and site at least hourly supports early detection to avoid or minimize potential impact of complications.

Central line–associated bloodstream infection (CLABSI) is defined as a primary bloodstream infection in a patient who had a central line within the 48-hour period before the development of the bloodstream infection and is not bloodstream related to an infection at another site (O'Grady et al., 2011). Numerous campaigns successfully directed at CLABSI prevention have included a bundled approach of simultaneously practiced strategies often in collaboration with other facilities (Fisher et al., 2013; Shepherd et al., 2015; Wilder, Wall, Haggard, & Epperson, 2016). Some of these bundle components included: hand hygiene, maximum sterile barrier precautions for insertion, a dedicated team, chlorhexidine for skin antisepsis, chlorhexidine-impregnated dressings, sterile tubing changes, two-person dressing changes, needleless connector scrub hygiene, closed medication systems, and daily evaluation of line necessity for timely removal of the line when no longer needed (Taylor et al., 2011; Wilder et al., 2016). A care bundle is a group of practices that individually impact outcomes but, when applied together, dramatically improve outcomes (Institute for Healthcare Improvement, 2016). The implementation of evidence-based central line care across statewide collaboratives has significantly reduced CLABSIs (Piazza et al., 2016; Shepherd et al., 2015).

Specially trained personnel play a key role in preventing and detecting complications (Holzmann-Pazgal et al., 2012; Legemaat, Jongerdena, van Rens, Zielman, & van den Hoogen, 2015; Taylor et al., 2011). Personnel who care for patients with central lines should receive specialized training in catheter insertion, care, and maintenance (O'Grady et al., 2011). While not every complication is preventable, the effects can be minimized by early detection. Frequent monitoring of vascular access sites at least hourly can play a critical role in managing complications and producing positive outcomes (Gorski et al., 2016; Wyckoff & Sharpe, 2015).

EVIDENCE-BASED PRACTICE FOR PICCs

Healthcare providers caring for infants with vascular access should be aware of the risks of complications, especially infection, and incorporate the latest evidence-based practice to support minimizing complications. It has been reported that 18 of every 100 babies experienced an iatrogenic event with 87% of these preventable, 20% due to catheters, and 15% due to nosocomial infection, with severely ill and small infants at highest risk (Kugelman et al., 2008; Srulovici et al., 2012). Practices regarding insertion, catheter tip location, care, and maintenance have traditionally reflected knowledge primarily gained from the adult and pediatric population. Fortunately, new evidence specific to neonates continues to emerge to drive evidence-based care for vascular devices in infants. The benefit of decreased risk of complications associated with optimal catheter tip location has been demonstrated (Colacchio, Deng, Northrup, & Bizzarro, 2012; Goldwasser et al., 2017). The implementation of a team approach using specially trained personnel has been associated with desirable outcomes (Wilder et al., 2016). Practices regarding appropriate device selection, catheter tip location, maintenance, and CLABSI prevention reflect evidence of successful strategies that continue to evolve and should be incorporated to continue to increase care outcomes.

TECHNOLOGICAL ADVANCES FOR PICCs

As technologic advances permit the miniaturization of equipment, greater options for PICC care are becoming available for safer insertion and maintenance of these tiny lifelines. The use of ultrasound, infrared technology, modern transilluminators, and modified Seldinger technique can facilitate PICC insertion and provide new solutions for locating and accessing challenging infant vasculature (Elkhunovich et al., 2017; Sharma, Farahbakhsh, & Tabatabaii, 2018).

REFERENCES

Alexander, M., Corrigan, A., Gorski, L., Hankins, J., & Perucca, R. (2010). *Infusion nursing: An evidence-based approach* (3rd ed.). St. Louis, MO: Saunders Elsevier.

Benjamin, D. K., Jr., Miller, W., Garges, H., Benjamin, D. K., McKinney, R. E., Jr., Cotton, M., . . . Alexander, K. A. (2001). Bacteremia, central catheters, and neonates: When to pull the line. *Pediatrics, 107*(6), 1272–1276. doi:10.1542/peds.107.6.1272

Butler-O'Hara, M., D'Angio, C. T., Hoey, H., & Stevens, T. P. (2012). An evidence-based catheter bundle alters central venous catheter strategy in newborn infants. *The Journal of Pediatrics, 160*(6), 972–977.e2. doi:10.1016/j.jpeds.2011.12.004

Chenoweth, K. B., Guo, J. W., & Chan, B. (2018). The extended dwell peripheral intravenous catheter is an alternative method of NICU

intravenous access. *Advances in Neonatal Care, 18*(4), 295–301. doi:10.1097/ANC.0000000000000515

Colacchio, K., Deng, Y., Northrup, V., & Bizzarro, M. J. (2012). Complications associated with central and non-central venous catheters in a neonatal intensive care unit. *Journal of Perinatology, 32*(12), 941–946. doi:10.1038/jp.2012.7

Elkhunovich, M., Barreras, J., Bock Pinero, V., Ziv, N., Vaiyani, A., & Mailhot, T. (2017). The use of ultrasound for peripheral IV placement by vascular access team nurses at a tertiary children's hospital. *Journal of Vascular Access, 18*(1), 57–63. doi:10.5301/jva.5000615

Fisher, D., Cochran, K. M., Provost, L. P., Patterson, J., Bristol, T., Metzguer, K., . . . McCaffrey, M. J. (2013). Reducing central line–associated bloodstream infections in North Carolina NICUs. *Pediatrics, 132*(6), e1664–e1671. doi:10.1542/peds.2013-2000

Food and Drug Administration. (1989). *Drug bulletin: Precautions necessary with central venous catheters*. Washington, DC: U.S. Government Printing Office.

Goldwasser, B., Baia, C., Kim, M., Taragin, B. H., & Angert, R. M. (2017). Non-central peripherally inserted central catheters in neonatal intensive care: Complication rates and longevity of catheters relative to tip position. *Pediatric Radiology, 47*(12), 1676–1681. doi:10.1007/s00247-017-3939-1

Gorski, L., Hadaway, L., Hagle, M., McGoldrick, M., Orr, M., & Doellman, D. (2016). Infusion therapy standards of practice. *Journal of Infusion Nursing, 39*(Suppl. 1S), S1–S159.

Gorski, L. A., Hagle, M. E., & Bierman, S. (2015). Intermittently delivered IV medication and pH: Reevaluating the evidence. *Journal of Infusion Nursing, 38*(1), 27–46. doi:10.1097/NAN.0000000000000081

Holzmann-Pazgal, G., Kubanda, A., Davis, K., Khan, A. M., Brumley, K., & Denson, S. E. (2012). Utilizing a line maintenance team to reduce central-line-associated bloodstream infections in a neonatal intensive care unit. *Journal of Perinatology, 32*(4), 281–286. doi:10.1038/jp.2011.91

Infusion Nurses Society. (2008). *Flushing protocols*. Norwood, MA: Author.

Infusion Nurses Society. (2011). *Infusion nursing standards of practice*. Norwood, MA: Wolters Kluwer Lippincott Williams & Wilkins.

Institute for Healthcare Improvement. (2016). *What is a bundle?* Retrieved from http://www.ihi.org/resources/Pages/ImprovementStories/WhatIsaBundle.aspx

Karadag-Oncel, E., Kara, A., Ozsurekci, Y., Arikan-Akdagli, S., Cengiz, A. B., Ceyhan, M., . . . Ozkaya-Parlakay, A. (2015). Candidaemia in a paediatric centre and importance of central venous catheter removal. *Mycoses, 58*(3), 140–148. doi:10.1111/myc.12288

Kugelman, A., Inbar-Sanado, E., Shinwell, E. S., Makhoul, I. R., Leshem, M., Zangen, S., . . . Bader, D. (2008). Iatrogenesis in neonatal intensive care units: Observational and interventional, prospective, multicenter study. *Pediatrics, 122*(3), 550–555. doi:10.1542/peds.2007-2729

Legemaat, M., Carr, P. J., van Rens, R. M., van Dijk, M., Poslawsky, I. E., & van den Hoogen, A. (2016). Peripheral intravenous cannulation: Complication rates in the neonatal population: A multicenter observational study. *Journal of Vascular Access, 17*(4), 360–365. doi:10.5301/jva.5000558

Legemaat, M. M., Jongerdena, I. P., van Rens, R. M. F. P. T., Zielman, M., & van den Hoogen, A. (2015). Effect of a vascular access team on central line-associated bloodstream infections in infants admitted to a neonatal intensive care unit: A systematic review. *International Journal of Nursing Studies, 52*(5), 1003–1010. doi:10.1016/j.ijnurstu.2014.11.010

Leick-Rude, M., & Haney, B. (2006). Midline catheter use in the intensive care nursery. *Neonatal Network, 25*(3), 189–199. doi:10.1891/0730-0832.25.3.189

O'Grady, N. P., Alexander, M., Burns, L. A., Dellinger, E. P., Garland, J., Heard, S. O., . . . Saint, S. (2011). Guidelines for the prevention of intravascular catheter-related infections. *Clinical Infectious Diseases, 52*(9), e162–e193. doi:10.1093/cid/cir138

Pettit, J. (2003). Assessment of the infant with a peripheral intravenous device. *Advances in Neonatal Care, 3*(5), 230–240. doi:10.1053/j.adnc.2003.08.006

Piazza, A. J., Brozanski, B., Provost, L., Grover, T. R., Chuo, J., Smith, J. R., . . . Pallotto, E. K. (2016). SLUG bug: Quality improvement with orchestrated testing leads to NICU CLABSI reduction. *Pediatrics, 137*(1), e20143642. doi:10.1542/peds.2014-3642

Said, M., & Rais-Bahrami, K. (2013a). Umbilical artery catheterization. In M. MacDonald, J. Ramasethu, & K. Rais-Bahrami (Eds.), *Atlas of procedures in neonatology* (5th ed., pp. 156–172). Philadelphia, PA: Lippincott Williams & Wilkins.

Said, M., & Rais-Bahrami, K. (2013b). Umbilical vein catheterization. In M. MacDonald, J. Ramasethu, & K. Rais-Bahrami (Eds.), *Atlas of procedures in neonatology* (5th ed., pp. 173–181). Philadelphia, PA: Lippincott Williams & Wilkins.

Sharma, D., Farahbakhsh, N., & Tabatabaii, S. A. (2018). Role of ultrasound for central catheter tip localization in neonates: A review of the current evidence. *Journal of Maternal-Fetal and Neonatal Medicine, 32*(14), 2429–2437. doi:10.1080/14767058.2018.1437135

Shepherd, E. G., Kelly, T. J., Vinsel, J. A., Cunningham, D. J., Keels, E., Beauseau, W., & McClead, R. E., Jr. (2015). Significant reduction of central-line associated bloodstream infections in a network of diverse neonatal nurseries. *Journal of Pediatrics, 167*(1), 41–46.e1–3. doi:10.1016/j.jpeds.2015.03.046

Srulovici, E., Ore, L., Shinwell, E. S., Blazer, S., Zangen, S., Riskin, A., . . . Kugelman, A. (2012). Factors associated with iatrogenesis in neonatal intensive care units: An observational multicenter study. *European Journal of Pediatrics, 171*(12), 1753–1759. doi:10.1007/s00431-012-1799-0

Taylor, T., Massaro, A., Williams, L., Doering, J., McCarter, R., He, J., . . . Short, B. (2011). Effect of a dedicated percutaneously inserted central catheter team on neonatal catheter-related bloodstream infection. *Advances in Neonatal Care, 11*(No. 2), 122–128. doi:10.1097/ANC.0b013e318210d059

Wilder, K. A., Wall, B., Haggard, D., & Epperson, T. (2016). CLABSI reduction strategy: A systematic central line quality improvement initiative integrating line-rounding principles and a team approach. *Advances in Neonatal Care, 16*(3), 170–177. doi:10.1097/ANC.0000000000000259

Wyckoff, M. (1999). Midline catheter use in the premature and full-term infant. *Journal of Vascular Access Devices, 4*(3), 26–29. doi:10.2309/108300899775970737

Wyckoff, M., & Sharpe, E. (2015). *Peripherally inserted central catheters: Guideline for practice* (3rd ed.). Chicago, IL: National Association of Neonatal Nurses.

VI

Newborn Whole-Body Cooling Protocol

Georgia R. Ditzenberger and Susan Tucker Blackburn

INTRODUCTION

Hypoxic ischemic encephalopathy (HIE) is an injury to the brain caused by systemic hypoxemia, ischemia, or a combination of the two conditions.

I. OBJECTIVE

To provide whole-body cooling to eligible newborns with HIE.

II. GENERAL INFORMATION

A. Whole-body cooling therapy will be provided to newborns meeting eligibility criteria. The neonatologist or pediatric neurologist will evaluate the newborn and determine whether the newborn meets the criteria for whole-body cooling.
B. The newborn will undergo whole-body cooling therapy to achieve and maintain an esophageal temperature of 33.5°C.
C. Cooling therapy is a 72-hour period of maintaining the esophageal body temperature at 33.5°C.
D. On completion of 72 hours of body cooling, the newborn will be rewarmed over a 6-hour period.
    1. A physician or neonatal nurse practitioner (NNP) must complete the whole-body cooling order set in the electronic chart to initiate this protocol.
    2. A physician or NNP must complete the rewarming order set in the electronic chart to initiate rewarming the newborn.
E. Risks to newborn
    1. Blood pressure changes: either hypo- or hypertension
    2. Respiratory pattern changes; may require ventilator support
    3. Abnormal clot formation
    4. Skin breakdown
    5. Metabolic acidosis

III. IMPLEMENTATION

A. Equipment and supplies
    1. Radiant warmer
    2. Electric cooling unit with a probe adapter cable and one set of connecting hoses
    3. One newborn-sized (22 × 33 inches) cooling blanket
    4. Two single patient use esophageal probes (one for esophageal temperature and one for skin temperature monitoring)
    5. Distilled/sterile water
    6. Tape to secure esophageal probe
B. Electric cooling unit set up: follow manufacturer's guidelines
    1. Fill the water reservoirs; monitor water level while unit is in use and add water as needed.
    2. Connect the hoses.
    3. Be sure the power switch is OFF prior to inserting the power plug into a grounded receptacle.
    4. Once the unit is plugged into a grounded receptacle, turn the unit on.
    5. Press and hold test lights button.
        a. Observe that all lights function properly.
        b. Confirm that the audible alarm sounds are functioning.
    6. Place the blanket on the radiant warmer.
    7. The blanket should be flat and the two hose clamps OPEN to allow the blanket to fill.
    8. Water will begin to circulate into the blanket.
        a. Check for leaks.
        b. Do not use pins or sharp objects on the blanket.
    9. After the blanket has filled, check the water level in the reservoir; refill as needed to keep the green line on the float visible.
    10. Do not overfill the reservoir.
C. Precool the blanket before the newborn is placed on the blanket.
    1. Operate the electric cooling unit in the manual control mode.
    2. Change the temperature scale by pressing the celsius/fahrenheit button to display "celsius."

3. Set the temperature desired to 33.5°C.
4. The unit will cool as required to bring the blanket temperature to the set point.

D. Temperature probes
1. Esophageal probe insertion
   a. Soften the esophageal probe prior to insertion by placing it in warm water for a few minutes.
   b. Do NOT use lubricants.
   c. Nasal placement of the probe is preferred.
   d. Position the esophageal temperature probe in the lower third of the esophagus.
   e. Measure the distance from the nares to the ear to the sternum minus 2 cm.
   f. Mark the probe with an indelible pen before inserting.
   g. Secure the probe by taping it to the newborn's nose.
   h. Probe position may be confirmed with the next routine chest radiographic examination.
   i. Connect the esophageal probe to the probe adapter cable and plug into the probe jack on the electric cooling unit.
2. Skin probe
   a. Position over abdomen; affix to skin with radiant warmer temperature probe reflective patch.
   b. Skin temperature probe and cable are compatible with the cardiorespiratory monitor and are connected directly into the monitor's temperature module.

E. Cooling the newborn
1. Place the newborn directly on the cooling blanket on the radiant warmer in supine position.
   a. The newborn's entire head and body should be resting on the cooling blanket.
   b. There should be nothing between the newborn and the cooling blanket (no receiving blankets, cloth diapers, gel pads, etc.).
2. The radiant warmer must be off.
3. Any other exogenous heat source must be off.
4. Change the electric cooling unit to automatic control mode.
   a. Make sure the set point is 33.5°C.
   b. The unit will cool as required to bring the newborn's esophageal temperature to the set point.

F. Maintain the set point at 33.5°C.
1. This is the desired esophageal temperature for the next 72 hours.
2. Once the newborn's esophageal temperature reaches the set point of 33.5°C, a single blanket layer, such as a thick receiving blanket, may be used between the newborn and the cooling blanket to minimize soiling the cooling blanket.
3. Patient temperature display will flash until the newborn's temperature is within 1°C of the set point.
4. Expect some fluctuation around the set point; it should not be more than ± 1°C.

G. Monitor temperatures
1. Record the esophageal, skin, axillary, and blanket water temperatures in the electronic patient record:
   a. Every 15 minutes for 2 hours
   b. Then every hour for 4 hours
   c. Then every 2 hours until completion of the 72 hours of cooling

H. Assess skin integrity, perfusion, vital signs, and potential complications every hour.

IV. REWARMING THE NEWBORN

A. Verify that the rewarming order set is in the electronic patient chart.
1. Newborn is rewarmed gradually, increasing the esophageal temperature at a rate of 0.5°C per hour over a 6-hour period.
   a. Every hour, increase the electric cooling unit set point by 0.5°C.
   b. During rewarming, temperatures should be recorded every hour until the skin temperature is stable at 36.5°C.
2. At the end of the 6-hour rewarming period, turn on the radiant warmer skin control 0.5°C higher than the newborn's current skin temperature.
3. Continue to increase the radiant warmer skin control by 0.5°C every hour until the newborn's axillary temperature is 36.5°C.
   a. Avoid rewarming any faster than 6 hours.
   b. Avoid axillary temperatures greater than 37°C.
4. Remove the cooling blanket from beneath the newborn.
5. Remove the esophageal probe and discard.

REFERENCES

Gunn, A. J., Battin, M. R., Gluckman, P. D., Gunn, T. R., & Bennet, L. (2005). Therapeutic hypothermia: From lab to NICU. *Neonatal Intensive Care, 19*, 35–40. doi:10.1515/JPM.2005.061

Shankaran, S., Laptook, A. R., Ehrenkranz, R. A., Tyson, J. E., McDonald, S. A., Donovan, E. F., . . . Jobe, A. H. (2005). Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. *New England Journal of Medicine, 353*(15), 1574–1584. doi:10.1056/NEJMcps050929

Verklan, M. T., & Walden, M. (Eds.). (2014). *Core curriculum for neonatal intensive care nursing* (5th ed.). St. Louis, MO: Mosby.

VII

Neuroprotective Interventions

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INTRODUCTION

There is ample evidence that neuroprotective family-centered developmental care in the neonatal intensive care unit (NICU) results in improved neonatal and neurodevelopmental outcomes, decreased lengths of stay, decreased costs, increased family satisfaction, and even enhanced employee satisfaction once a culture of change has been accomplished (Als et al., 1994; Als et al., 2004; Altimier & Phillips, 2013; Cooper, Gallagher, Sternesky, Ledsky, & Berns, 2007; Melnyk et al., 2006; Phillips, 2015). However, implementing the known principles of neuroprotective family-centered developmental care in the NICU and creating the needed culture changes have often been fraught with internal and external challenges.

The earlier in gestation a baby is born, the more vulnerable is its fragile brain and the more critical it is to provide effective and consistent neuroprotective care from the moment of birth to protect and support optimal brain development. Because developmental care is primarily about neuroprotection (although it affects many other aspects of infant development), the term *neuroprotection* is utilized throughout these guidelines and interventions. The creation of neuroprotective interventions as guidelines for NICUs to implement within their units should be based on the most up-to-date, evidence-based best practices that are supported by research and literature, as well as subject matter expertise. Recognizing that the need for neuroprotective care is ongoing and dynamic, each guideline should include an overall goal, recommendations, rationale, supporting data, and measures of accountability. Any long-term change involving new knowledge, skills, and behaviors will take time and meticulous planning, as well as adequate resources and administrative support to make sure new practices will be adopted by all.

Neuroprotective developmental care is grounded in evidence by research from a number of disciplines including nursing, medicine, neuroscience, and psychology (Als, 2009; Altimier, Kenner, & Damus, 2015; Bastani, Rajai, Farsi, & Als, 2017; Bergman, 2015; Burnett, Cheong, & Doyle, 2018; Gao, Lin, Grewen, & Gilmore, 2017; Montirosso et al., 2016). Improvements in health outcomes, neurodevelopment, lengths of stays, hospital costs, as well as staff and parent satisfaction have been documented when neuroprotective education and subsequent change of care practices were implemented (Altimier, 2015a, 2015b; Altimier et al., 2015; Altimier, Eichel, Warner, Tedeschi, & Brown, 2005; Cardin et al., 2015; Coughlin, 2008; Dungca, Allison, & Watson, 2011; Hendricks-Muñoz & Mayers, 2014; Hendricks-Muñoz, Prendergast, Caprio, & Wasserman, 2002; Liaw, Yang, Chang, Chou, & Chao, 2009; Lockridge, 2018; Ludwig, Steichen, Khoury, & Krieg, 2008; Phillips, 2015).

For the implementation of neuroprotective developmental care to be successful, all NICU staff must have the knowledge and skills to effectively implement this care, and there must be cooperation and collaboration between all healthcare providers and ancillary and support staff. Additional organizational support from the executive leadership team and nursing, medical, allied health, and support services is warranted. While practice changes can be arbitrarily imposed by administration, sustained cultural change rarely occurs in this manner. In order to establish neuroprotective family-centered developmental care as the norm in any unit, all staff that are affected by changes in care should be intimately involved, and at the least represented in the process. Guidelines should provide flexibility to support individual organizational needs, yet be structured enough to provide clear expectations for their implementation in order to hold all staff accountable. In addition to time and effort spent on teaching neuroprotective caregiving skills, it is worthwhile to spend time on evaluating the amount of changes occurring currently in the NICU as well as the level of motivation and team building attitudes among the multidisciplinary staff who will be implementing those skills.

Despite the stressors that accompany an ever-changing environment, many staff appear to manage the effects of perceived stressors and continue to deliver high-quality care, while others struggle. People experience stress when they perceive that events are placing excessive demands on them. Perceptions determine whether a given situation is experienced as an excessive demand or perceived as a challenging task or an opportunity, and these perceptions depend on the way in which an individual interprets the situation.

Multiple environmental changes experienced concurrently in a NICU can cause perceptions of work-related stress, which can lead to high staff turnover, decreased engagement, and decreased satisfaction. Environmental stressors in the nursing profession

include unpredictable staffing and scheduling, lack of role clarity, low involvement in decision making, and poor support, which are all likely to increase the level of stress and lead to job burnout. Studies reveal that the perception of stress in the practice environment has a direct impact on patient safety, patient experience, and staff decision making, as well as staff health and well-being, and can lead to burnout and ultimately affect productivity and employee retention (Braithwaite, 2008; Carter & Tourangeau, 2012; Larrabee et al., 2010; Pannell & Rowe, 2017).

One of the most popular models presenting how environmental stressors translate into the experience of stress has been developed by Lazarus and Folkman (1984). In that model, stress is defined as a relationship with the environment that exceeds an individual's ability to cope. Resilience is a self-regulatory mechanism and has been recognized as a significant personality factor involved in the process of coping. Resilience has been defined as a mental characteristic conducive to endurance, flexible adjustment, and mobilization to act in problematic situations (Ogińska-Bulik & Juczyński, 2008). Resilience helps tolerate negative emotions and experienced failures. Stress resilience can help an individual move forward in a positive way while maintaining equilibrium and some sense of control over his or her environment, despite significant stress or adversity (Larrabee et al., 2010). Resilience may be an important resource protecting nurses against negative effects of occupational stress. Research has demonstrated that sources of resilience include two main factors—personal factors and environmental-systemic factors. Interaction between these two factors contributes to the emergence of resilience and resilient attributes (Herrman et al., 2011), traits that are important to actively cultivate in any environment where rapid change is occurring.

While experiencing a high level of stress, nurses frequently deny the existence of difficult situations and additionally blame themselves for their emergence. Denial and self-blame, which are both maladaptive coping strategies, are categorized as escape and avoidance coping strategies (Carver & Connor-Smith, 2010). There are numerous difficult situations in the NICU that nurses experience, such as deterioration of an infant's health, complicated diagnoses, and death of a patient, as well as complicated family situations. Denial is a unique strategy used at the beginning of a stressful situation and it may prove beneficial due to temporary distance to the situation. Nevertheless, it disturbs and prevents effective coping. Self-blame, on the other hand, is a strategy manifesting helplessness, and it is defined as criticizing oneself for stressful circumstances. Utilizing self-blame and/or denial as coping strategies is not conducive to adjusting to difficult situations and actually is conducive to anxiety, depression, and overall poor mental health among nurses (Mark & Smith, 2011).

Mróz (2015) found a negative correlation between perceived stress and resilience. Results indicated that a low level of perceived stress is related to a high level of resilience, showing that the ability to adapt to and solve problems in a flexible manner is conducive to perceiving various problems as not stressful (Mróz, 2015). Similar results have proven that resilience interpreted as positive thinking, flexibility, assuming responsibility, and separating work and life is conducive to the ability to maintain the work–life balance among nurses (Kim & Windsor, 2015). Resilience also protects nurses against development of the symptoms of posttraumatic stress disorder (PTSD; Mealer, Jones, & Moss, 2012), and the level of perceived stress and job burnout (Mróz, 2014).

Benner's Novice to Expert model states that a bedside nurse is considered an expert after 5 years of nursing experience (Benner, 1984). It is frequently believed that more tenured nurses have more life and clinical experiences, and therefore can more easily develop stress resiliency. Findings from recent studies contradict this belief and find no correlation between age, experience, and resiliency (Lowe, 2013; Pannell & Rowe, 2017; Rushton, Batcheller, Schroeder, & Donohue, 2015). Nurses who have learned to adapt and thrive in the midst of adversity are recognized as resilient. Resilience is an attribute that can be developed and enhanced through education and support. Characteristics implemented by resilient nurses to cope with challenging work environments included supportive social networks, optimism, having a resilient role model, and a spiritual frame of reference (Mealer et al., 2012).

Although skills are critical in nursing, they may not be the key factor in reducing the perception of work-related stress. Enhanced critical thinking and decision-making skills, augmented composure and ability to function under stress, improved personal confidence, increased ability to listen more fully and nonreactively, and augmented feelings of empowerment in supportive and caring work environments may be the key to stress resilience.

Knoster's Managing Complex Change Model is a useful framework to utilize when introducing transformational change management principles in busy work environments. According to Knoster, there are six key elements required for effective change: vision, consensus, skills, incentives, resources, and an action plan (Knoster, 1995). To drive complex changes successfully, an organization needs to activate all six components, defined as follows:

VISION

The key to an effective strategy is to create a vision within a defined architecture. A vision is a clearly imagined view of the end state of change. No change should proceed without a clear vision of the goal and an understanding of the strategic path required to get there. A vision should convey two things: where you are going, and why you are going there. Building a shared vision is a critical factor in managing change. It is the starting point for goals and provides the launch pad for action and the parameters for problem solving.

Without a strategic vision, there will be *confusion* and therefore a lack of direction.

Structure in processes and in the organization is necessary to drive a strategic vision. Gaps in necessary policies, procedures, and/or guidelines must first be identified. Time must be spent early in the process to create interprofessional evidence-based best practices within the structure of policies, procedures, and guidelines that include defined standards and accountability metrics for all staff to follow. These must be organized, communicated, implemented, and audited for compliance in an organized fashion with clearly delineated expectations. Strong leadership is necessary to facilitate and sustain a cultural transformation.

CONSENSUS

Consensus includes cooperation, collaboration, and collegiality.

- Cooperation—agreement on ideas, values, purposes, shared understanding
- Collaboration—working together in an atmosphere of support and encouragement
- Collegiality—development of a learning community gaining skills and expertise together

Without consensus, there will be *sabotage*, where unwilling or unconvinced staff can actively work against the willing. Negativity of counterarguments can drag everyone down and prevent action.

SKILLS

Any cultural change requires a change in behaviors. Staff, and people in general, easily revert to old behaviors (habits) given the opportunity. Ensuring that new, changed behaviors take hold is where education and training come into play. A comprehensive training program is suggested in order to hardwire new skills required for staff to work in the "new" environment and to fulfill the new vision. Once the vision is established and the structure is identified, it is necessary to build the skills needed to realize the vision.

Without the appropriate competencies and skills needed to achieve the vision, there will be *anxiety*. Anxiety is inevitable in those who feel they do not have the necessary knowledge or expertise to cope with or to implement new situations, and also in those that have little faith in the training to provide them with knowledge and skills. Fear is a key generator of resistance to change and providing the opportunity to acquire needed skills is a key mitigating factor.

INCENTIVES

After the "Why?" in vision, the most common question those affected by change will ask is, "What's in it for me?" Incentives should spring directly from the vision for the organizational change. While rewards are given for accomplishments achieved, incentives are enticements to accomplish the change. Incentives can be intrinsic or extrinsic and can help motivate the workforce to acquire and maintain new skills. The types of incentives required to produce cultural change are those that impact the work itself. Incentives to change must be commensurate with the level of change demanded. Streamlining workflows and simplifying ease of use is a huge incentive and far more likely to be accepted than non–work-related incentives.

Without incentives, there will be *resistance* from those who see nothing in the changes for them, no moral meaning, no personal meaning, and/or no benefit. Resistant staff have the conviction that things are just fine as they are and see no need to change. If the change is perceived to increase the burden on individuals for an extended period, resistance, along with frustration and anxiety, will increase.

RESOURCES

In addition to meticulous planning, any significant change in culture or practices will also require a commitment by hospital administration and clinical leadership to allocate adequate resources needed, allowing the vision to be achieved. Resources include everything—and everyone—needed to make the change happen, such as the following:

- Physical resources
- Any items that people feel are necessary to enable them to make the required changes
- Use of existing knowledge or expertise within the organization or outside it
- Existing staff used as a resource, including management team members
- Emotional or social support/collegiality
- Development of knowledge, expertise, and skills through effective training programs
- Extra staffing
- New equipment
- Time given to development, planning, and reflection

Without the necessary resources, there will be *frustration*. If teams do not have the tools, money, time, information, and people necessary to adequately implement the changes needed to ensure success, outcomes will remain the same and the team will become frustrated and lose faith in the possibility of successful change. It is common for clinical leadership to create a vision that is shared by staff, but does not have the endorsement and backing of hospital administration and therefore lacks the resources needed to implement or maintain the change. Without administrative support, a change significant enough to improve patient or family outcomes is unlikely. It is critically important to include hospital administration and clinical leadership early in the process of designing and planning any significant change process.

ACTION PLAN

The action plan, based on specific achievable goals and objectives, is a way to make sure your organization's vision is made concrete. The action plan must spell out how the goals are to be reached, articulate who is responsible, specify the desired results and outcomes, and lay out a timeline for achieving the goals. The results of each action plan demonstrated through an organized cycle of improvement, such as the PDSA (Plan, Do, Study, Act) cycle, and their impact on the vision must be shared, communicated, and, if at all possible, published.

Action planning is a continuous thread across all phases—it is the change process. Although presented as the final component of the change framework, it should be viewed as the foundation of the systems' transformational change process. Clearly understood metrics for accountability are necessary for success. Rewards and consequences must be established for holding staff accountable to the action plan.

Without an action plan, staff feel like they are on a never-ending *treadmill*, doing what they have always done in the way they have always done it and therefore not succeeding in working in new ways, and not achieving new goals.

CREATING A CULTURE OF CHANGE

Organizational change is essentially cultural change, which demands shifts in behavior and beliefs. Staff typically go through the stages of acculturation as they accept (or reject) the newly established culture. Utilizing a team-based framework, the authors define acculturation as a two-way process where both cultures (the old and the new ways of working) come together to create one desired unit culture. Values are transferred, and beliefs are adopted to create behavioral changes necessary to achieve the vision. Acculturated staff become stakeholders in the process and engage in the transformational change.

The Knoster model is a helpful way for planning and operationalizing, studying and evaluating, as well as diagnosing what might be needed when plans go awry. Often, there is a sense that something is wrong with the change process, but no one understands how to resolve or determine the root of the problem. The Knoster model is a powerful tool to connect the symptom with the missing or misappropriated components of change, make a diagnosis, and propose a therapeutic recommendation. If those leading the process of change fail to put any one of these elements in place, the change efforts will not succeed as intended and may fail.

Implementing neuroprotective interventions (NPIs) as outlined in the Neonatal Integrative Developmental Care Model framework requires such a plan. Defining NPIs is just a start. To fully incorporate the identified NPIs into a unit's culture, a thorough process of transformational change is required. Milette, Martel, da Silva, and Coughlin McNeil (2017a, 2017b) outline several existing organizational implementation strategies for developmental care, including the NIDCAP program (Als et al., 1994), the Wee Care Neuroprotective NICU program (Altimier et al., 2015), and strategies outlined by Coughlin (2016), which were modelled from the Wee Care Program (Milette et al., 2017a, 2017b). Utilizing Knoster's Managing Complex Change Model with organizational leaders across the world, the Wee Care Neuroprotective NICU program, NPIs, and Small Baby Guidelines have all been operationalized with measurable criteria and attributes, and each has demonstrated success (Altimier et al., 2015; Altimier & Phillips, 2018; Cardin et al., 2015; Coughlin, 2008; Dungca et al., 2011; Hendricks-Muñoz et al., 2002; Lockridge, 2018; Ludwig et al., 2008; Phillips, 2015).

The Neonatal Integrative Developmental Care Model utilizes NPIs as strategies to support optimal synaptic neural connections, promote normal development, and prevent disabilities. Seven neuroprotective core measures for family-centered developmental care of the premature neonate are depicted on petals of a lotus as the Healing Environment, Partnering with Families, Positioning and Handling, Safeguarding Sleep, Minimizing Stress and Pain, Protecting Skin, and Optimizing Nutrition. The overlapping petals of the model demonstrate the integrative nature of developmental care (see Figure VII.1).

Each core measure has a standard(s) with a policy or protocol that guides care of the infant/family as it relates to that specific core measure. Corresponding infant characteristics, which are measurable reflections of the desired core measure outcomes, are identified, and specific goals target the improvements/outcomes desired. Clinical applications include NPIs that define and specify the actions required to meet the goal(s). These must be evidence-based, reliably applied, and scientifically valid.

A description of each core measure, along with teamwork and collaboration, is reviewed in detail in "The Neonatal Integrative Developmental Care Model: Advanced Clinical Applications of the Seven Core Measures for Neuroprotective Family-Centered Developmental Care" (Altimier & Phillips, 2016). Table VII.1 further details the NPIs outlined by Altimier and Phillips (2016), with an expanded scope, given the dynamic nature of neuroprotective care.

SUMMARY

Organizational change happens naturally all the time for better or for worse. When there is a specific aim—like the implementation of NPIs—there must be specific efforts in change management to align an organization's culture (i.e., beliefs and ways of behaving) to the new interventions or change practices. The Knoster model provides a solid framework, comprised of components that are easily remembered but no more easily accomplished than any other model. No organizational change model is perfect. No one model can guarantee a desired outcome. Only the change champions in an organization and those who take part in the change can make the outcomes align with the vision that forms the basis for the future state. Resistance to change is a natural reaction when people are asked to do something they have not done before, or perhaps even more when they are asked to do something they have done before, but in a different way. Overcoming the associated symptoms, confusion, sabotage, anxiety, resistance, frustration, and, treadmill effect is the aim of great organizational change management, however it is accomplished.

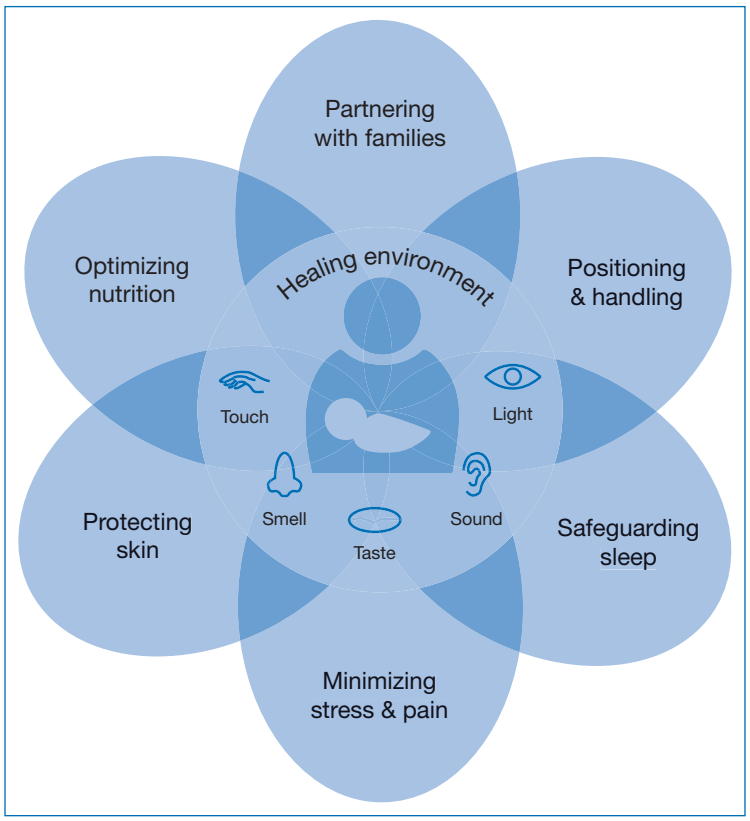


FIGURE VII.1 Neonatal integrative developmental care model.

TABLE VII.1

PROTOCOL FOR THE IMPLEMENTATION OF NEUROPROTECTIVE INTERVENTIONS FOR INFANTS IN THE NICU RELATED TO THE SEVEN CORE MEASURES OF NEUROPROTECTIVE FAMILY-CENTERED DEVELOPMENTAL CARE

Core Measure # 1: Healing Environment

(Altimier, 2015b; Altimier & Phillips, 2013, 2018; Altimier & White, 2019; Bergman, 2015; Craig et al., 2015; S. Hall, Hynan, et al., 2015; Phillips, 2015, 2019; Robison, 2003; White, Smith, & Shepley, 2013)

Standard: A policy/procedure/guideline on the Healing Environment including physical space and privacy as well as the protection of the infant's sensory system exists and is followed throughout the infant's stay.

Infant Characteristics	Goals	Neuroprotective Interventions
Stability of the infant's autonomic, sensory, motoric, and state regulation systems	An environment will be maintained that promotes healing by minimizing the impact of the artificial extrauterine NICU environment on the developing infant's brain. The central role of mother/parent will be recognized and prioritized as the developmentally expected environment for all newborn mammals.	**General** • Educate, coach, and mentor parents on the importance of creating a healing environment that protects the developing sensory system of the preterm infant. Emphasize their central role in the healing environment as parents and as active members of the caregiving team. **Skin-to-Skin Contact** • Facilitate early, frequent, and prolonged SSC, recognizing that SSC with mother/parent is the developmentally expected habitat for all newborn mammals. • Make zero separation between parents and infant a priority whenever possible. • Provide comfortable and safe reclining chair or adult bed for early, frequent, and prolonged SSC. **Space** • Maintain a private and safe environment for the infant and family that consists of a minimum of 120 square feet per patient. • Provide organized, uncluttered space for the family in order to support comfortable and private caregiving interactions with their baby. • When renovations are planned, advocate for single family rooms and promote utilization of the latest standards from the *Recommended Standards for Newborn ICU Design* at www3.nd.edu/~nicudes. **Tactile** • Provide a neutral thermal environment for the infant incorporating the following factors: Facilitate early, frequent, and prolonged SSC. • If ELBW, provide humidity during the first 2 weeks after birth (50% humidity is provided to the infant in SSC). • Provide care in SSC or incubator until infant can maintain own temperature. **Vestibular** • Change infant's position gently and slowly without sudden movements. • Eliminate moving infant beds to different spaces to accommodate staffing patterns. **Olfactory** • Maintain a scent-free and fragrance-free unit. • Minimize exposure to noxious odors. • Expose infant to mother's scent via SSC, breast pad, soft cloth, or Snoedel.

(*continued*)

TABLE VII.1

PROTOCOL FOR THE IMPLEMENTATION OF NEUROPROTECTIVE INTERVENTIONS FOR INFANTS IN THE NICU RELATED TO THE SEVEN CORE MEASURES OF NEUROPROTECTIVE FAMILY-CENTERED DEVELOPMENTAL CARE (*continued*)

Infant Characteristics	Goals	Neuroprotective
		Gustatory • Position infant with hands near face. • Provide colostrum or expressed MOM oral care per protocol. • Provide positive oral feeding experiences as outlined in Optimizing Nutrition section. **Auditory** • Support infants with consistently calm, relaxing environment with muted sounds and lighting between and during caregiving interactions. • Be mindful of own voice and other sounds produced in the NICU. • Monitor sound levels to maintain sound levels of <50 decibels. • Silence alarms as quickly as possible and avoid unnecessary alarms. • Comfort crying infants as quickly as possible. • Expose infant to audible maternal/paternal voice, encouraging parents to quietly talk and sing to their infant. **Visual** • Provide adjustable light levels up to a maximum of 60 fc. • Gently shield infant's eyes during care if overhead light is needed. • Be mindful of structuring an infant's visual field to support alert wakefulness as appropriate, transition to sleep, or quiet, restful sleep. • Minimize purposeful visual stimulation until 37 weeks' gestation. **Overall Healing Environment** • Consider all sources of light, sound, movement, smell, and taste confronting an infant during care and eliminate all inappropriate or unnecessary sources of stimulation. • Create and implement an individualized developmental care plan for each infant. • Provide guidance to parents on how to create and sustain a healing environment with respect to sensory exposures and experiences. • When renovating the NICU environment, advocate for optimal family support spaces and resource supports.

(*continued*)

TABLE VII.1

PROTOCOL FOR THE IMPLEMENTATION OF NEUROPROTECTIVE INTERVENTIONS FOR INFANTS IN THE NICU RELATED TO THE SEVEN CORE MEASURES OF NEUROPROTECTIVE FAMILY-CENTERED DEVELOPMENTAL CARE (*continued*)

Core Measure # 2: Partnering With Families

(Altimier et al., 2015a; Altimier & Phillips, 2013, 2018; Altimier & White, 2019; Bergman, 2014, 2015; Craig et al., 2015; Hall, Ryan, Beatty, & Grubbs, 2015; Kenner, Press, & Ryan, 2015; Phillips, 2019; Purdy, Craig, & Zeanah, 2015; Sullivan & Altimier, 2007)

Standard 1: A policy/procedure/guideline on Partnering With Families to include unlimited access to ensure round-the-clock information and access to their baby exists and is followed throughout the infant's stay.
Standard 2: There is a specific mission statement addressing Partnering With Families.
Standard 3: NICU staff are competent in educating, coaching, and mentoring parents in infant caregiving skills and in providing psychosocial support to NICU families.

Infant Characteristics	Goals	Neuroprotective Interventions
Infant's response to parental interactions	• Family-centered care is supported from birth or as soon as a NICU stay is anticipated (antenatally if possible). • Parents will be viewed not as "visitors" but as equal and vital members of the caregiving team with zero separation supported and encouraged (24 hours/day). • Parents will be supported and encouraged as the primary and most important caregivers for their infant, incorporating them as full participatory, essential healing partners within the NICU caregiving team. • Infant will develop emotional connection and secure attachment with parents. • Parents who lose a baby before, during, or shortly after birth, or later in the NICU, will be supported at all points of care.	• Make zero separation between parents and infant a priority. • Facilitate early, frequent, and prolonged SSC, recognizing that SSC supports secure bonds of attachment between parents and their infant, which is necessary for normal development. • Support families in a warm, respectful, and welcoming manner. • Actively listen to families' feelings and concerns (both verbal and nonverbal) and respond with appropriate action when needed. • Accommodate the presence of families in the NICU and encourage participation in medical rounds and nursing handoffs. • Provide parents with full access and input to both written and electronic medical records with medical interpretation as needed. • Communicate the infant's medical, nursing, and developmental needs in a culturally appropriate and understandable way. • Share information with families in a tone of voice that preserves confidentiality. • Educate, coach, and mentor parents in becoming active participants in their baby's care in supporting their infant's optimal development. • Educate parents on infant attachment, developmental, and safety issues. • Encourage families to personalize their infant's bed space and make the NICU environment more homelike. • Support breast milk expression and breastfeeding. • Include and support sibling and extended family participation as desired by parents. • Provide social networking opportunities for parents of premature infants in the NICU. • Provide peer-to-peer support with parents who have gone through similar NICU stays. • A Family Advisory Council will be consulted for involvement in the design of P & P, and deign strategies. • Honor both Health Insurance Portability and Accountability Act and safety concerns while in the NICU. • Encourage and empower parents as they develop confidence in their own abilities to continue caring for their baby when going home. • Provide staff education related to principles of family-centered care and how to support parents' caregiving roles. • Acknowledge where the family is in regard to stages of grief and loss and provide individualized and appropriate resources as needed. • Provide anticipatory guidance regarding the increased risks of anxiety and depression commonly experienced by NICU parents, recognizing they all may handle the NICU experience differently. • Provide psychosocial support for all members of the family, including grandparents and the baby's siblings, and make referrals to professional resources as needed.

(*continued*)

TABLE VII.1

PROTOCOL FOR THE IMPLEMENTATION OF NEUROPROTECTIVE INTERVENTIONS FOR INFANTS IN THE NICU RELATED TO THE SEVEN CORE MEASURES OF NEUROPROTECTIVE FAMILY-CENTERED DEVELOPMENTAL CARE (*continued*)

Core Measure # 3: Positioning and Handling

(Altimier et al., 2015; Altimier & Phillips, 2013, 2016, 2018; Charafeddine et al., 2018; Craig et al., 2015; Danner-Bowman & Cardin, 2015; Hunter, Lee, & Altimier, 2015; Jeanson, 2013; Phillips, 2015; Robison, 2003; Spilker & Rosenblum, 2016)

Standard: A policy/procedure/guideline on Positioning and Handling exists and is followed throughout the infant's stay that includes educating, coaching, and mentoring parents on how to position and handle their infant.

Infant Characteristics	Goals	Neuroprotective Interventions

• Autonomic stability during handling
• Ability to maintain tone and flexed postures with and without supports
	• Autonomic stability will be maintained throughout positioning changes and handling activities as well as during periods of rest and sleep.
	• Parents will be educated, coached, and mentored in how to position and handle their infant.
	• Preventable positional deformities will be eliminated or minimized by maintaining infants in a midline, flexed, contained, and comfortable position throughout their NICU stay.
	• The caregiver sees herself or himself in partnership with the baby so that caregiving procedures are performed "with" the infant rather than "to" the infant.
	• Infants will be provided developmentally appropriate stimulation/play as they mature (i.e., mobiles, swings, etc.).
		• Facilitate early, frequent, and prolonged SSC, recognizing that SSC promotes optimal flexed positioning in full ventral contact with parent's chest, enhancing warmth and physiologic stability.
		• Anticipate, prioritize, and support the infant's individualized needs during each caregiving interaction to minimize stressors known to interfere with normal development.
		• Educate staff (medical, nursing, and therapists) about the importance of doing cares or procedures "with" the infant, not "to" the infant. Support staff in seeing the infant as an active participant in the caregiving activity or procedure.
		• Educate, coach, and mentor parents in how to position, contain, and handle their infant in a developmentally appropriate manner.
		• Educate parents how to engage with their infant when doing caregiving activities so as to make an emotional connection rather than simply to complete a task.
		• Provide infants with positioning supports needed to maintain optimal tone and position and to remain either in a quiet, restful sleep or a relaxed, comfortable wakeful state.
		• Utilize a validated and reliable positioning assessment tool (i.e., Infant Positioning Assessment Tool [IPAT]) routinely to ensure appropriate positioning and encourage accountability.
		• Maintain a midline, flexed, contained, and comfortable position at all times utilizing appropriate positioning aids and boundaries.
		• Promote hand to mouth/face contact.
		• Provide appropriate ventral support when infant is prone to ensure flexed shoulders/hips.
		• Avoid doing procedures with infant in a prone position where he/she is unable to use self-comforting abilities.
		• Provide swaddling when bathing and weighing to reduce stress.
		• Let behavioral cues of stress or relaxation guide infant care.
		• Assess infant sleep–wake cycle to evaluate appropriate timing of positioning and caring.
		• Reposition infant with cares and minimally every 4 hours.
		• Provide four-handed support during positioning and caring activities of extremely preterm infants.
		• When providing caregiving activities,
		  • Collect all supplies prior to approaching infant so infant is not left unattended or unsupported once hands-on care has begun.
		  • Seek another person to support infant care during a potentially stressful experience, including bathing and weighing.
		  • Include parents in providing support when available and willing.

(*continued*)

TABLE VII.1

PROTOCOL FOR THE IMPLEMENTATION OF NEUROPROTECTIVE INTERVENTIONS FOR INFANTS IN THE NICU RELATED TO THE SEVEN CORE MEASURES OF NEUROPROTECTIVE FAMILY-CENTERED DEVELOPMENTAL CARE (*continued*)

Core Measure # 4: Safeguarding Sleep

(Altimier & Phillips, 2013, 2016; Altimier & White, 2019; Craig et al., 2015; Graven, 2006; Graven & Browne, 2008)

Standard 1: A policy/procedure/guideline on Safeguarding Sleep exists and is followed throughout the infant's stay.
Standard 2: A policy/procedure/guideline on Safe Sleep Practices exists and is followed prior to discharge.

Infant Characteristics	Goals	Neuroprotective Interventions
• Infant sleep–wake states, cycles, and transitions • Infant's maturity and readiness for Back-to-Sleep protocol	• Infant sleep–wake states will be assessed before initiating all caregiving activities. • Prolonged periods of uninterrupted sleep will be protected. • Infants will be transitioned to Back-to-Sleep protocol when developmentally appropriate.	• Educate all NICU staff (medical, nursing, and therapists) about the importance of sleep for normal infant brain development. • Educate, coach, and mentor parents on sleep–wake states and how to promote sleep in their infant, recognizing the importance of sleep to healing, growth, and brain development. • Facilitate early, frequent, and prolonged SSC, recognizing that SSC promotes development of more mature sleep cycles. • Utilize a validated and reliable scale to assess sleep–wake states to promote sleep and plan caregiving activities. • Protect quiet sleep states by providing flexibility in timings of care. Individualize all caregiving activities by clustering cares based on infant sleep–wake states. Take care not to overstress infant with too many clustered cares at once. • If necessary, to arouse a sleeping infant, approach using a soft voice/whisper followed by gentle touch. • Support smooth transitions back to restful sleep with supportive positioning and containment before stepping away from bedside. • Promote a quiet environment to ensure uninterrupted sleep. • Protect the eyes from direct light exposure and maintain low levels of ambient light. • Use incubator covers to protect the infant from direct light. • Provide some daily exposure to light, preferably including shorter wavelengths, for entrainment of the circadian rhythm. • Avoid (when possible) high doses of sedatives and drugs that can depress the endogenous firing of cells, thus interfering with visual development, rapid and non–rapid eye movement sleep cycles, and, therefore, optimal brain development. • Provide developmental care appropriate for the age and maturation of the infant, including supportive positioning for very preterm infants, to promote restful sleep. • Assure infant is able to maintain normal sleep pattern during Back-to-Sleep well before discharge and role model this behavior in the NICU. • Provide tummy time/prone-to-play time routinely for infants that are on Back-to-Sleep protocol. • Coach, educate, and mentor parents about the importance and rationale for Safe Sleep practices and tummy time.

(*continued*)

TABLE VII.1

PROTOCOL FOR THE IMPLEMENTATION OF NEUROPROTECTIVE INTERVENTIONS FOR INFANTS IN THE NICU RELATED TO THE SEVEN CORE MEASURES OF NEUROPROTECTIVE FAMILY-CENTERED DEVELOPMENTAL CARE (*continued*)

Core Measure # 5: Minimizing Stress and Pain		
(Altimier & Phillips, 2013, 2016, 2018; Benoit et al., 2016; Craig et al., 2015; Johnston et al., 2014; Phillips, 2015, 2019; Robison, 2003)		
Standard: A policy/procedure/guideline on the assessment and management of pain exists and is followed throughout the infant's stay.		
Infant Characteristics	**Goals**	**Neuroprotective Interventions**
Behavioral cues indicating stress or self-regulation	Promote self-regulation and neurodevelopmental organization.	• Acknowledge the many sources of stress and pain in the developmentally unexpected and artificial environment of the NICU for preterm and sick infants. • Educate all NICU staff (medical, nursing, and therapists) how to recognize infant behavioral signs of stress and pain for preterm and term infants and how to utilize developmentally appropriate comfort measures. • Facilitate early, frequent, and prolonged SSC, recognizing that the infant's stress level is usually significantly lower when in SSC with parents. • Educate, coach, and mentor parents on infant behavioral cues related to stress and pain and how to provide their infant with nonpharmacologic support during stressful or painful procedures. • Utilize a validated and reliable pain assessment tool to evaluate the need for pharmacologic support. • Provide nonpharmacologic support (SSC, breast milk, sucrose, pacifier) with all minor invasive interventions. • Provide midline, flexion, and containment with all positioning to promote comfort. • Provide therapeutic positioning aids to promote supportive positioning. • Use swaddling for weighing and bathing to reduce stress. • Provide individualized care in a manner that anticipates, prioritizes, and supports the needs of infants to minimize stress and pain. • Talk softly to babies before, during, and after a painful or stressful procedure or caregiving event to provide forewarning and sympathy, and to let them know when the procedure is over.

(*continued*)

TABLE VII.1

PROTOCOL FOR THE IMPLEMENTATION OF NEUROPROTECTIVE INTERVENTIONS FOR INFANTS IN THE NICU RELATED TO THE SEVEN CORE MEASURES OF NEUROPROTECTIVE FAMILY-CENTERED DEVELOPMENTAL CARE (*continued*)

Core Measure # 6: Protecting Skin		
(Altimier & Phillips, 2013, 2016, 2018; Craig et al., 2015; Phillips, Chantry, & Gallagher, 2005; Robison, 2003; Visscher, Adam, Brink, & Odio, 2015; Visscher & Narendran, 2014)		
Standard: A policy/procedure/guideline on Skin Care exists and is followed throughout the infant's stay.		
Infant Characteristics	**Goals**	**Neuroprotective Interventions**
Maturity and integrity of infant skin	• Reduce transepidermal water loss of ELBW infants. • Maintain skin integrity of the infant from birth to discharge. • Provide developmentally appropriate infant massage.	• Facilitate early, frequent, and prolonged SSC, recognizing that the skin is a conduit of nerve impulses to the brain; thus, healthy, intact skin promotes brain development. • Educate, coach, and mentor parents on skin care, swaddled bathing, and delivery of developmentally appropriate infant massage. • Provide parents with guidance on how to protect their baby's skin and its many functions, including its role as a conduit of neurosensory information to the brain. • Utilize a validated and reliable skin assessment tool (i.e., Braden Q) on admission and routinely according to hospital protocol. • Provide individualized care in a manner that anticipates, prioritizes, and supports the needs of infants to optimize neuromotor development. • Provide humidity for ELBW infants during the first 2 weeks after birth (50% humidity is provided with SSC). • Provide appropriate positioning support utilizing gel products when needed to prevent skin breakdown. • Examine position of nasal prongs per protocol to protect against breakdown of nasal septum. • Minimize use of adhesives and use caution when removing adhesives to prevent epidermal stripping. • Avoid soaps and routine use of emollients. • Use water only for bathing infants $<$1,000 g. • Use pH neutral cleansers for bathing infants $>$1,000 g. • When bathing, do swaddled bathing in bed or tub (to reduce stress and promote relaxation) with overhead warmer (to prevent risk of hypothermia). • Priority should be given to parents to bathe their infant whenever possible. • Provide bathing no more than every 72–96 hours.

(*continued*)

TABLE VII.1

PROTOCOL FOR THE IMPLEMENTATION OF NEUROPROTECTIVE INTERVENTIONS FOR INFANTS IN THE NICU RELATED TO THE SEVEN CORE MEASURES OF NEUROPROTECTIVE FAMILY-CENTERED DEVELOPMENTAL CARE (*continued*)

Core Measure # 7: Optimizing Nutrition

(Altimier & Phillips, 2013, 2016, 2018; Craig et al., 2015; Hall, Ryan, et al., 2015; Purdy et al., 2015; Robison, 2003)

Standard 1: A policy/procedure/guideline on Optimizing Nutrition (cue-based/infant-driven breastfeeding or bottlefeeding), which includes infant readiness, quality of feeding, and caregiver techniques, is followed throughout the infant's stay.
Standard 2: A policy/procedure/guideline on SSC (kangaroo care) exists and is followed throughout the infant's stay.

Infant Characteristics	Goals	Neuroprotective Interventions
• Physiologic stability with feeding and handling • Feeding readiness cues • Coordinated suck/swallow/breathing throughout breastfeeding or bottlefeeding • Endurance to maintain nutritional intake and support growth	• Feeding will be safe, functional, nurturing, and developmentally appropriate. • Optimized nutrition will be enhanced by individualizing all feeding care practices. • Oral aversions will be prevented by ensuring that eating is a positive experience for infants. • Infants of breastfeeding mothers will be competent at breastfeeding prior to discharge.	• Support and encourage the expression of MOM to support an optimum milk supply. • Facilitate early, frequent, and prolonged SSC, recognizing that SSC causes a spike in prolactin, thus facilitating milk production, and promotes earlier initiation as well as longer duration of breastfeeding. • Minimize negative perioral stimulation (adhesives, suctioning, etc.). • Utilize indwelling gavage tubes rather than intermittent tubes. • Promote positive oral stimulation and NNS at mother's breast during gavage feeds (no need for breasts to be pumped for very preterm infants). • Provide taste and smell of breast milk through oral care with gavage feedings when mother is not present, holding infant and using an appropriately sized pacifier for NNS. • Utilize a validated and reliable Infant-Driven Readiness—Feeding—Caregiving Scale. • Individualize care by incorporating cue-based/infant-driven feeding practices. • Ensure every feeding experience is a positive, pleasant, and nurturing experience. • Promote side-lying position close to parent/caregiver when bottlefeeding. • Educate, coach, and mentor parents about infant feeding cues, and guide them with pacing and other feeding techniques to provide positive and supportive oral feeding experiences for their infant. • Encourage preterm infants to practice suckling when in SSC whenever they are interested. • Support and encourage breastfeeding well before discharge. • Have a discharge feeding plan in place before discharge, including outpatient breastfeeding support if needed.

(*continued*)

TABLE VII.1

PROTOCOL FOR THE IMPLEMENTATION OF NEUROPROTECTIVE INTERVENTIONS FOR INFANTS IN THE NICU RELATED TO THE SEVEN CORE MEASURES OF NEUROPROTECTIVE FAMILY-CENTERED DEVELOPMENTAL CARE (*continued*)

Teamwork and Collaboration

(Altimier et al., 2015; Altimier & Phillips, 2016; Axelin, Outinen, Lainema, Lehtonen, & Franck, 2018; Craig et al., 2015; Gausvik, Lautar, Miller, Pallerla, & Schlaudecker, 2015; Hall, Cross, et al., 2015; Hall, Cross, et al., 2015; Hall, Ryan, et al., 2015; Robison, 2003; Rushton et al., 2015)

Standard 1: An interdisciplinary team of caregivers, supported by clinical leadership and hospital administration, works together collaboratively to support the infant's and family's goals.
Standard 2: Hospital leadership facilitates education related to self-care of all NICU staff to prevent burnout, compassion fatigue, and secondary PTSD.
Standard 3: A policy/procedure/guideline on roles and responsibilities of team members and collaboration exists and is followed.

Infant Characteristics	Goals	Neuroprotective Interventions
Infant and family are central to each team member's plans, decisions, and caregiving	• An individualized developmentally appropriate environment is provided for every infant and family. • NICU staff feel supported by hospital administration, clinical leadership, and by their peers in providing optimal neuroprotective family-centered developmental care to infants and families. • Parents feel supported in their NICU experience, feel valued as full and active members of the NICU team, and feel assured that their baby is getting the best medical and developmental care possible.	• Educate all staff about the principles and practices of neuroprotective family-centered developmental care. • Support and value parents as the primary caregivers by educating, coaching, and mentoring parents to be active members of the NICU caregiving team. • Incorporate structured interdisciplinary rounding (to include parents) into the team's practice. • Provide as much space and comfort as possible for family involvement in caregiving, keeping charts and equipment well organized and avoiding clutter. • Include parents in all medical and nursing decision making. • Share pertinent information with colleagues, as appropriate, about family involvement, strengths, and challenges in relation to their infant's NICU stay. • Develop strategies to provide psychosocial support for NICU parents as needed. • Respect and support the roles of other individuals and disciplines when caring for infants, and support each other through mentoring relationships. • Prior to performing a procedure, care, or examination on an infant under the care of another team member (or parent), discuss needs of that team member to mutually agree on the timing. • Consistently share information about the infant's behavioral competencies, vulnerabilities, and thresholds when communicating with colleagues during rounds or shift change. • Willingly and proactively assist colleagues to provide support for infants in their care during potentially stressful care activities or painful procedures. • Ensure all infants and families are treated consistently with support, dignity, and respect by all team members, and constructively confront team members (staff or parents) if discrepancies are noted. • Educate staff on the differences and value of cultural practices other than their own. • Educate staff on optimal methods of communication with parents in distress. • Educate staff on elements of self-care to proactively prevent and minimize burnout, compassion fatigue, and secondary PTSD. • Ensure that channels of communication between nursing staff and their supervisors are clear with an outlet to access support. • Educate staff about methods for improving and expanding family-centered developmental care in the NICU, including ongoing assessments and quality improvement projects. • Ensure support from hospital administration and clinical leadership to share in the vision and provide needed resources for funding, education, equipment, and personnel. • Plan and schedule team building activities to encourage interdisciplinary professional relationships among staff, maintain motivation for ongoing collaboration, and inspire future improvements.

ELBW, extremely low birth weight; MOM, mother's own milk; NICU, neonatal intensive care unit; NNS, nonnutritive sucking; PTSD, posttraumatic stress disorder; SSC, skin-to-skin contact.

REFERENCES

Als, H. (2009). NIDCAP: Testing the effectiveness of a relationship-based comprehensive intervention. *Pediatrics, 124*(4), 1208–1210. doi:10.1542/peds.2009-1646

Als, H., Duffy, F. H., McAnulty, G. B., Rivkin, M. J., Vajapeyam, S., Mulkern, R. V., . . . Eichenwald, E. C. (2004). Early experience alters brain function and structure. *Pediatrics, 113*(4), 846–857. doi:10.1542/peds.113.4.846

Als, H., Lawhon, G., Duffy, F. H., McAnulty, G. B., Gibes-Grossman, R., & Blickman, J. G. (1994). Individualized developmental care for the very-low-birth-weight preterm infant: Medical and neurofunctional effects. *Journal of the American Medical Association, 272*(11), 853–858. doi:10.1001/jama.1994.03520110033025

Altimier, L. (2015a). Compassionate family care framework: A new collaborative compassionate care model for NICU families and caregivers. *Newborn and Infant Nursing Reviews, 15*(1), 33–41. doi:10.1053/j.nainr.2015.01.005

Altimier, L. (2015b). Neuroprotective core measure 1: The healing environment. *Newborn and Infant Nursing Reviews, 15*(3), 89–94. doi:10.1053/j.nainr.2015.06.014

Altimier, L., Kenner, C., & Damus, K. (2015). The effect of a comprehensive developmental care training program: Wee Care neuroprotective program (Wee Care) on seven neuroprotective core measures for family-centered developmental care of premature neonates. *Newborn and Infant Nursing Reviews, 15*(1), 6–16. doi:10.1053/j.nainr.2015.01.006

Altimier, L., & Phillips, R. M. (2013). The Neonatal Integrative Developmental Care Model: Seven neuroprotective core measures for family-centered developmental care. *Newborn and Infant Nursing Reviews, 13*(1), 9–22. doi:10.1053/j.nainr.2012.12.002

Altimier, L., & Phillips, R. M. (2016). The Neonatal Integrative Developmental Care Model: Advanced clinical applications of the seven core measures for neuroprotective family-centered developmental care. *Newborn and Infant Nursing Reviews, 16*(4), 230–244. doi:10.1053/j.nainr.2016.09.030

Altimier, L., & Phillips, R. M. (2018). Neuroprotective care of extremely preterm infants in the first 72 hours after birth. *Critical Care Nursing Clinics of North America, 30*, 563–583. doi:10.1016/j.cnc.2018.07.010

Altimier, L. B., Eichel, M., Warner, B., Tedeschi, L., & Brown, B. (2005). Developmental care: Changing the NICU physically and behaviorally to promote patient outcomes and contain costs. *Neonatal Intensive Care, 18*(4), 12–16.

Altimier, L. B., & White, R. D. (2019). The neonatal intensive care unit (NICU) environment. In C. Kenner, M. Boykova, & L. B. Altimier (Eds.), *Comprehensive neonatal nursing care* (6th ed.). New York, NY: Springer Publishing Company.

Axelin, A., Outinen, J., Lainema, K., Lehtonen, L., & Franck, L. (2018). Neonatologists can impede or support parents' participation in decision-making during medical rounds in neonatal intensive care units. *Acta Pædiatrica, 107*(12), 2100–2108. doi:10.1111/apa.14386

Bastani, F., Rajai, N., Farsi, Z., & Als, H. (2017). The effects of kangaroo care on the sleep and wake states of preterm infants. *Journal of Nursing Research, 25*(3), 231–239. doi:10.1097/JNR.0000000000000194

Benner, P. (1984). *From novice to expert: Excellence and power in clinical nursing practice*. Menlo Park, CA: Addison-Wesley.

Benoit, B., Campbell-Yeo, M., Johnston, C., Latimer, M., Caddell, K., & Orr, T. (2016). Staff nurse utilization of kangaroo care as an intervention for procedural pain in preterm infants. *Advances in Neonatal Care, 16*(3), 229–238. doi:10.1097/ANC.0000000000000262

Bergman, N. J. (2014). The neuroscience of birth—And the case for zero separation. *Curationis, 37*(2), 1–4. doi:10.4102/curationis.v37i2.1440

Bergman, N. J. (2015). Skin-to-skin contact as a neurosupportive measure. *Newborn and Infant Nursing Reviews, 15*(3), 145–150. doi:10.1053/j.nainr.2015.06.006

Braithwaite, M. (2008). Nurse burnout and stress in the NICU. *Advances in Neonatal Care, 8*(6), 343–347. doi:10.1097/01.ANC.0000342767.17606.d1

Burnett, A., Cheong, J., & Doyle, L. W. (2018). Biological and social influences on the neurodevelopmental outcomes of preterm infants. *Clinics in Perinatology, 45*(3), 485–500. doi:10.1016/j.clp.2018.05.005

Cardin, A., Rens, L., Stewart, S., Danner-Bowman, K., McCarley, R., & Kopsas, R. (2015). Neuroprotective core measures 1–7: A developmental care journey: Transformations in NICU design and caregiving attitudes. *Newborn and Infant Nursing Reviews, 15*(3), 132–141. doi:10.1053/j.nainr.2015.06.007

Carter, M. R., & Tourangeau, A. E. (2012). Staying in nursing: What factors determine whether nurses intend to remain employed?. *Journal of Advanced Nursing, 678*(7), 1589–1600. doi:10.1111/j.1365-2648.2012.05973.x

Carver, C. S., & Connor-Smith, J. (2010). Personality and coping. *Annual Review of Psychology, 61*, 679–704. doi:10.1146/annurev.psych.093008.100352

Charafeddine, L., Masri, S., Ibrahim, P., Badin, D., Cheayto, S., & Tamim, H. (2018). Targeted educational program improves infant positioning practice in the NICU. *International Journal for Quality in Health Care, 30*(9), 642–648. doi:10.1093/intqhc/mzy123

Cooper, L. G., Gooding, J. S., Gallagher, J., Sternesky, L., Ledsky, R., & Berns, S. D. (2007). Impact of family-centered care initiative on NICU care, staff and families. *Journal of Perinatology, 27*, S32–S37. doi:10.1038/sj.jp.7211840

Coughlin, M. (2008). Quality caring in the neonatal intensive care unit: The effectiveness of the Wee Care program. *Neonatal Intensive Care, 21*(5), 30–32.

Coughlin, M. (2016). *Trauma-informed care in the NICU: Evidence-based practice guidlines for neonatal clinicians*. New York, NY: Springer Publishing Company.

Craig, J. W., Glick, C., Phillips, R., Hall, S. L., Smith, J., & Browne, J. (2015). Recommendations for involving the family in developmental care of the NICU baby. *Journal of Perinatology, 35*(Suppl. 1), S5–S8. doi:10.1038/jp.2015.142

Danner-Bowman, K., & Cardin, A. (2015). Neuroprotective core measure 3: Positioning & handling—A look at preventing positional plagiocephaly. *Newborn and Infant Nursing Reviews, 15*(3), 111–113. doi:10.1053/j.nainr.2015.06.009

Dungca, C. U., Allison, M., & Watson, G. (2011). Developmental care in the neonatal intensive care unit-New York City Health and Hospitals Corporation (HHC). *Neonatal Intensive Care, 24*(2), 18–19.

Gao, W., Lin, W., Grewen, K., & Gilmore, J. H. (2017). Functional connectivity of the infant human brain: Plastic and modifiable. *The Neuroscientist, 23*, 169–184. doi:10.1177/1073858416635986

Gausvik, C., Lautar, A., Miller, L., Pallerla, H., & Schlaudecker, J. (2015). Structured nursing communication on interdisciplinary acute care teams improves perceptions of safety, efficiency, understanding of care plan and teamwork as well as job satisfaction. *Journal of Multidisciplinary Healthcare, 8*, 33–37. doi:10.2147/JMDH.S72623

Graven, S. N. (2006). Sleep and brain development. *Clinics in Perinatology, 33*(3), 693–706. doi:10.1016/j.clp.2006.06.009

Graven, S. N., & Browne, J. V. (2008). Sleep and brain development: The critical role of sleep in fetal and early neonatal brain development. *Newborn and Infant Nursing Reviews, 8*(4), 173–179. doi:10.1053/j.nainr.2008.10.008

Hall, S., Hynan, M., Phillips, R., Press, J., Kenner, C., & Ryan, D. J. (2015). Development of program standards for psychosocial support of parents of infants admitted to a neonatal intensive care unit: A National Interdisciplinary Consensus Model. *Newborn and Infant Nursing Reviews, 15*(1), 24–27. doi:10.1053/j.nainr.2015.01.007

Hall, S. L., Cross, J., Selix, N. W., Patterson, C., Segre, L., Chuffo-Siewert, R., . . . Martin, M. L. (2015). Recommendations for enhancing psychosocial support of NICU parents through staff education and support. *Journal of Perinatology, 35*(Suppl. 1), S29–S36. doi:10.1038/jp.2015.147

Hall, S. L., Ryan, D. J., Beatty, J., & Grubbs, L. (2015). Recommendations for peer-to-peer support for NICU parents. *Journal of Perinatology, 35*(Suppl. 1), S9–S13. doi:10.1038/jp.2015.143

Hendricks-Muñoz, K. D., & Mayers, R. M. (2014). A neonatal nurse training program in kangaroo mother care (KMC) decreases barriers to KMC utilization in the NICU. *American Journal of Perinatology, 31*(11), 987–991. doi:10.1055/s-0034-1371359

Hendricks-Muñoz, K. D., Prendergast, C., Caprio, M., & Wasserman, R. (2002). Developmental care: The impact of Wee Care developmental care training on short-term infant outcome and hospital costs. *Newborn and Infant Nursing Reviews, 2*(1), 39–45. doi:10.1053/nbin.2002.31492

Herrman, H., Stewart, D. E., Diaz-Granados, N., Berger, D., Phil, E. L., Jackson, B., & Yuen, T. (2011). What is resilience? *LaRevue Canadienne de Psychiatrie, 56*, 258–265. doi:10.1177/070674371105600504

Hunter, J., Lee, A., & Altimier, L. (2015). Neonatal intensive care unit. In J. Case-Smith & J. C. O'Brien (Eds.), *Occupational therapy for children and adolescents* (7th ed., pp. 595–635). St. Louis, MO: Elsevier.

Jeanson, E. (2013). One-to-one bedside nurse education as a means to improve positioning consistency. *Newborn and Infant Nursing Reviews, 13*(1), 27–30. doi:10.1053/j.nainr.2012.12.004

Johnston, C., Campbell-Yeo, M., Fernandes, A., Inglis, D., Streiner, D., & Zee, R. (2014). Skin-to-skin care for procedural pain in neonates. *The Cochrane Database of Systematic Reviews*, (1), CD008435. doi:10.1002/14651858.CD008435.pub2

Kenner, C., Press, J., & Ryan, D. (2015). Recommendations for palliative and bereavement care in the NICU: A family-centered integrative approach. *Journal of Perinatology, 35*(Suppl. 1), S19–S23. doi:10.1038/jp.2015.145

Kim, M., & Windsor, C. (2015). Resilience and work-life balance in first-line nurse manager. *Asian Nursing Research, 9*, 21–27. doi:10.1016/j.anr.2014.09.003

Knoster, T. (1995). Factors in managing complex change. In R. A. Villa & J. S. Thousand (Eds.), *Creating an inclusive school*. Alexandria, VA: Association for Supervision and Curriculum Development.

Larrabee, J. H., Wu, Y., Persily, C. A., Simoni, P. S., Johnston, P. A., Marcischak, T. L., . . . Gladden, S. D. (2010). Influence of stress resiliency on RN job satisfaction and intent to stay. *Western Journal of Nursing Research, 31*(1), 81–102. doi:10.1177/0193945909343293

Lazarus, R., & Folkman, S. (1984). *Stress, appraisal, and coping*. New York, NY: Springer Publishing Company.

Liaw, J., Yang, L., Chang, L., Chou, H., & Chao, S. (2009). Improving neonatal caregiving through a developmentally supportive care training program. *Applied Nursing Research, 22*(2), 86–93. doi:10.1016/j.apnr.2007.05.001

Lockridge, T. (2018). Neonatal neuroprotection. *MCN: The American Journal of Maternal Child Nursing, 43*(2), 66–76. doi:10.1097/NMC.0000000000000411

Lowe, L. D. (2013). Creating a caring work environment and fostering nurse resiliency. *International Journal of Human Caring, 17*(4), 52–59. doi:10.20467/1091-5710.17.4.52

Ludwig, S., Steichen, J., Khoury, J., & Krieg, P. (2008). Quality improvement analysis of developmental care in infants less than 1500 grams at birth. *Newborn and Infant Nursing Reviews, 8*(2), 94–100. doi:10.1053/j.nainr.2008.03.011

Mark, G., & Smith, A. (2011). Occupational stress, job characteristics, coping, and the mental health of nurses. *British Journal of Health Psychology, 17*(3), 505–521. doi:10.1111/j.2044-8287.2011.02051.x

Mealer, M., Jones, J., & Moss, M. (2012). A qualitative study of resilience and posttraumatic stress disorder in United States ICU nurses. *Intensive Care Medicine, 38*(9), 1445–1451. doi:10.1007/s00134-012-2600-6

Melnyk, B. M., Feinstein, N. F., Alpert-Gillis, L., Fairbanks, E., Crean, H. F., Sinkin, R. A., . . . Gross, S. J. (2006). Reducing premature infants' length of stay and improving parents' mental health outcomes with the Creating Opportunities for Parent Empowerment (COPE) neonatal intensive care unit program: A randomized, controlled trial. *Pediatrics, 111*(5), e1414–e1427. doi:10.1542/peds.2005-2580

Milette, I., Martel, M., da Silva, M., & Coughlin McNeil, M. (2017a). Guidelines for the institutional implementation of developmental neuroprotective care in the neonatal intensive care unit. Part A: Background and rationale. *Canadian Journal of Nursing Research = Revue Canadienne De Recherche En Sciences Infirmières, 49*(2), 46–62. doi:10.1177/0844562117706882

Milette, I., Martel, M., da Silva, M., & Coughlin McNeil, M. (2017b). Guidelines for the institutional implementation of developmental neuroprotective care in the NICU. Part B: Recommendations and justification. *Canadian Journal of Nursing Research = Revue Canadienne De Recherche En Sciences Infirmières, 49*(2), 63–74. doi:10.1177/0844562117708126

Montirosso, R., Giusti, L., Prete, A., Zanini, R., Bellù, R., & Borgatti, R. (2016). Does quality of developmental care in NICUs affect health-related quality of life in 5-year-old children born preterm? *Pediatric Research, 80*(6), 824–828. doi:10.1038/pr.2016.158

Mróz, J. (2014). Resilience, perceived stress and types of work-related behavior and experience among nurses. *Hygeia Public Health, 49*(4), 857–863.

Mróz, J. (2015). Predictive roles of coping and resilience for the perceived stress in nurses. *Progress in Health Sciences, 5*(2), 77–84.

Ogińska-Bulik, N., & Juczyński, Z. (2008). The resiliency assessment scale (SPP-25). *Nowiny Psychologiczne, 3*, 39–56.

Pannell, L., & Rowe, L. (2017). Stress resiliency practices in neonatal nurses. *Advances in Neonatal Care, 17*(4), 274–281. doi:10.1097/ANC.0000000000000366

Phillips, R. M. (2015). Seven core measures of neuroprotective family-centered developmental care: Creating an infrastructure for implementation. *Newborn and Infant Nursing Reviews, 15*(3), 4. doi:10.1053/j.nainr.2015.06.004

Purdy, I. B., Craig, J. W., & Zeanah, P. (2015). NICU discharge planning and beyond: Recommendations for parent psychosocial support. *Journal of Perinatology, 35*, S24–S28. doi:10.1038/jp.2015.146

Robison, L. D. (2003). An organizational guide for an effective developmental program in the NICU. *Journal of Obstetric, Gynecologic, and Neonatal Nursing: JOGNN / NAACOG, 32*(3), 379–386. doi:10.1177/0884217503253536

Rushton, C. H., Batcheller, J., Schroeder, K., & Donohue, P. (2015). Burnout and resilience among nurses practicing in high-intensity settings. *American Journal of Critical Care, 24*(5), 412–420. doi:10.4037/ajcc2015291Am

Spilker, A. H., Hill, C., & Rosenblum, R. (2016). The effectiveness of a standardised positioning tool and bedside education on the developmental positioning proficiency of NICU nurses. *Intensive & Critical Care Nursing, 35*, 10–15. doi:10.1016/j.iccn.2016.01.004

Sullivan, P., & Altimier, L. (2007). Creating a family advisory council. *Newborn & Infant Nursing Reviews, 7*(1), 3–6. doi:10.1053/j.nainr.2006.12.011

Visscher, M., Adam, R., Brink, S., & Odio, M. (2015). Newborn infant skin: Physiology, development, and care. *Clinics in Dermatology, 33*(3), 271–280. doi:10.1016/j.clindermatol.2014.12.003

Visscher, M., & Narendran, V. (2014). Neonatal infant skin: Development, structure and function. *Newborn and Infant Nursing Reviews, 14*(4), 135–141. doi:10.1053/j.nainr.2014.10.004

White, R., Smith, J., & Shepley, M. (2013). Recommended standards for newborn ICU design, eighth edition. *Journal of Perinatology, 33*(Suppl. 1), S2–S16. doi:10.1038/jp.2013.10

APPENDIX A

Neonatal Nurses and Interconception Care

Merry-K. Moos

INTRODUCTION

Healthcare providers and policy makers are increasingly aware that efforts to prevent reproductive casualties that begin in prenatal care are starting too late to affect primary prevention (Centers for Disease Control and Prevention [CDC], 2006). As a result, preconception and interconception cares have become a focus for healthcare interactions with women of childbearing age. Preconception and interconception health are defined as "Any intervention provided to women of childbearing age, regardless of pregnancy desire, to improve the health outcomes of women, newborns and children" (Dean et al., 2012). Knowledge of interconception care is important for NICU nurses because of their ongoing interactions with individual women when they visit their infants. This ongoing relationship allows the NICU nurse to observe the new mother's health status, her self-care practices, and her use of health and medical resources. Thus, the nurse may observe a woman becoming withdrawn, depressed, or anxious; she may observe that she is missing meals or stress eating; the nurse may note lack of sleep and lack of support.

Identification of a new mother's healthcare needs gives the NICU staff the opportunity to provide education, guidance, and support to the mother as they perform their usual care. NICU nurses can help identify maternal medical needs and health risks and assist new mothers in addressing their own health even as they focus on the well-being of their neonate.

Examples for each include the following:

- Strategies for taking care of self include encouraging
  - Time away from unit to eat meals
  - Healthy snacks
  - Taking breaks to walk in and around the hospital
  - Talking about her feelings about the baby's situation and encourage discussing fears, concerns, self-blame with the unit social worker and with her usual provider.
- Strategies for minimizing risks to women's own health and future reproductive outcomes include encouraging:
  - Women to maintain or become smoke free
  - Healthy approaches to stress reduction
  - Waiting the optimal time (18–60 months) before becoming pregnant again (Conde-Agudelo, Rosas-Bermudez, & Kafury-Goeta, 2006)
  - Attending postpartum visit(s) with healthcare provider
  - Use of an over-the-counter (OTC) daily multivitamin with folic acid after prenatal vitamins are depleted
  - Follow up with their usual provider for any medical needs identified during pregnancy (e.g., severe preeclampsia resulting in extreme prematurity, diabetes mellitus resulting in respiratory distress syndrome in infant, etc.)
  - Early identification and referral for signs and symptoms of anxiety and depressive disorder
  - Take the lead in linking a woman with the unit social worker or other resources as indicated for her own well-being

ONLINE RESOURCES

Before, Between and Beyond Pregnancy: The National Preconception/Interconception Curriculum and Resources Guide for Clinicians. Retrieved from http://www.beforeandbeyond.org

Information for women, families, and clinicians interested in preconception health can be retrieved from http://www.cdc.gov/preconception

http://www.marchofdimes.com/professionals/medicalresources.html; https://www.marchofdimes.org/nursing/index.bm2?cid=00000003; https://www.marchofdimes.org/pregnancy/before-pregnancy.aspx: Many relevant CNE opportunities can be accessed at this address including:

Preconception Health Promotion: The Foundation for a Healthier Tomorrow. A slide module for nurses on the content and evidence around preconception care.

Birth Spacing: An Evidence-based Strategy to Reduce Prematurity: An article about interconception intervals, strategies to impact and opportunities to keep activities patient-centered.

REFERENCES

Centers for Disease Control and Prevention. (2006). Recommendations for improving preconception health and health care: United States: A report of the CC/ATSDR Preconception Workgroup and the Select Panel on preconception care. *Morbidity and Mortality Weekly Report, 55,* 1–23.

Conde-Agudelo, A., Rosas-Bermudez, A., & Kafury-Goeta, A. C. (2006). Birth spacing and risk of adverse perinatal outcomes: A meta-analysis. *Journal of the American Medical Association, 295*(15), 1809–1823. doi:10.1001/jama.295.15.1809

Dean, S., Bhutta, Z., Mason, M. E., Howson, C., Chandra-Mouli, V., Lassi, Z., & Imam, A. (2012). Care before and between pregnancy. In C. P. Howson, M. V. Kinney, & J. E. Lawn (Eds.), *Born too soon: The global action report on preterm birth*. Geneva, Switzerland: World Health Organization.

APPENDIX B

Conversion Table to Standard International (SI) Units

Component	Present Unit	×	Conversion Factor	=	SI Unit
Clinical Hematology					
Erythrocytes	per mm^3		1		10^6/L
Hematocrit	%		0.01		(1)vol RBC/vol whole blood
Hemoglobin	g/dL		10		g/L
Leukocytes	per mm^3		1		10^6/L
Mean corpuscular hemoglobin concentration (MCHC)	g/dL		10		g/L
Mean corpuscular volume (MCV)	μm^3		1		fL
Platelet count	$10^3/mm^3$		1		10^9/L
Reticulocyte count	%		10		10^{-3}
Clinical Chemistry					
Acetone	mg/dL		0.1722		mmol/L
Albumin	g/dL		10		g/L
Aldosterone	ng/dL		27.74		pmol/L
Ammonia (as nitrogen)	µg/dL		0.7139		µmol/L
Bicarbonate	mEq/L		1		mmol/L
Bilirubin	mg/dL		17.1		µmol/L
Calcium	mg/dL		0.2495		mmol/L

Component	Present Unit	×	Conversion Factor	=	SI Unit
Calcium ion	mEq/L		0.50		mmol/L
Carotenes	µg/dL		0.01836		µmol/L
Ceruloplasmin	mg/dL		10.0		mg/L
Chloride	mEq/L		1		mmol/L
Cholesterol	mg/dL		0.02586		mmol/L
Complement, C_3 or C_4	mg/dL		0.01		g/L
Copper	µg/dL		0.1574		µmol/L
Cortisol	µg/dL		27.59		nmol/L
Creatine	mg/dL		76.25		µmol/L
Creatinine	mg/dL		88.40		µmol/L
Digoxin	ng/mL		1.281		nmol/L
Epinephrine	pg/mL		5.458		pmol/L
Fatty acids	mg/dL		10.0		mg/L
Ferritin	ng/mL		1		µg/L
α-Fetoprotein	ng/mL		1		µg/L
Fibrinogen	mg/dL		0.01		g/L
Folate	ng/mL		2.266		nmol/L
Fructose	mg/dL		0.05551		mmol/L
Galactose	mg/dL		0.05551		mmol/L
Gases					
PO_2	mm Hg (= torr)		0.1333		kPa
PCO_2	mm Hg (= torr)		0.1333		kPa
Glucagon	pg/mL		1		ng/L
Glucose	mg/dL		0.05551		mmol/L
Glycerol	mg/dL		0.1086		mmol/L
Growth hormone	ng/mL		1		µg/L
Haptoglobin	mg/dL		0.01		g/L

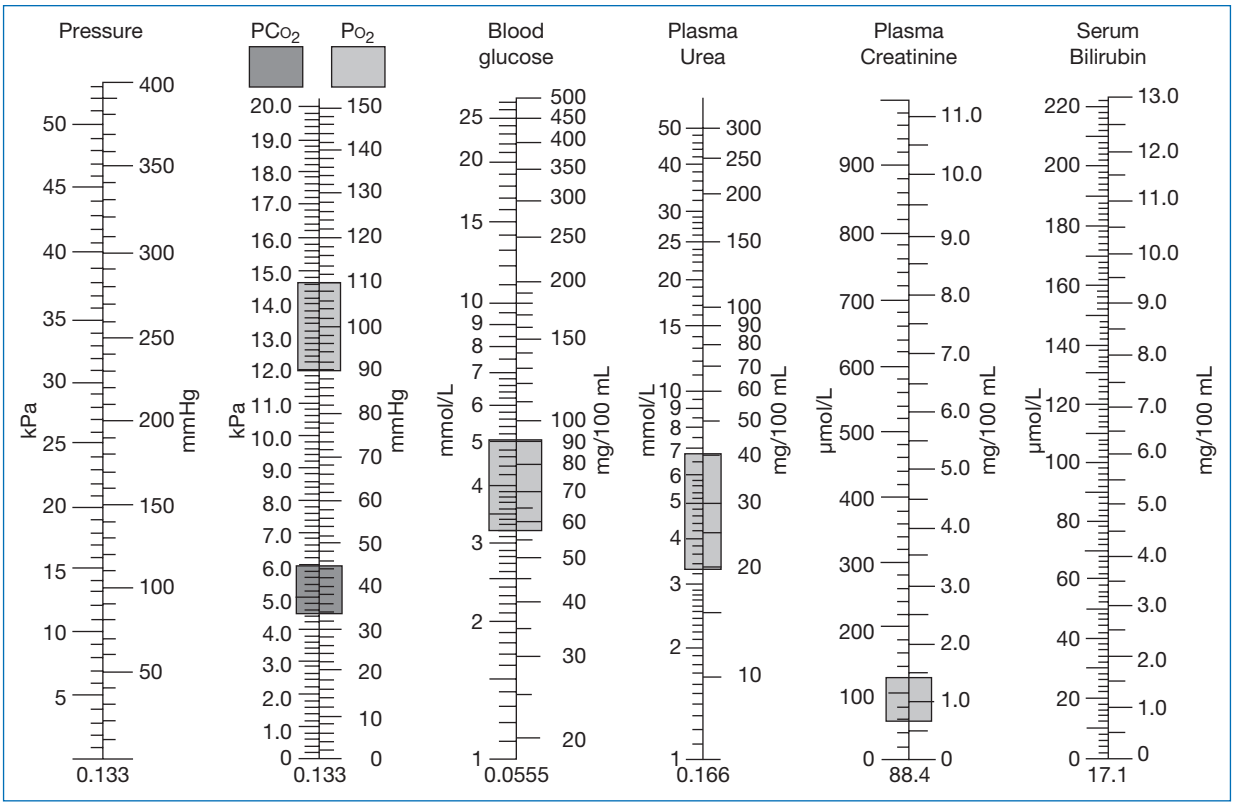
Component	Present Unit	×	Conversion Factor	=	SI Unit
Hemoglobin	g/dL		10		g/L
Insulin	µg/L		172.2		pmol/L
	mU/L		7.175		pmol/L
Iron	µg/dL		0.1791		µmol/L
Iron-binding capacity	µg/dL		0.1791		µmol/L
Lactate	mEq/L		1		mmol/L
Lead	µg/dL		0.04826		µmol/L
Lipoproteins	mg/dL		0.02586		mmol/L
Magnesium	mg/dL		0.4114		mmol/L
	mEq/L		0.50		mmol/L
Osmolality	mOsm/kg H_2O		1		mmol/kg H_2O
Phenobarbital	mg/dL		43.06		µmol/L
Phenytoin	mg/L		3.964		µmol/L
Phosphate	mg/dL		0.3229		mmol/L
Potassium	mEq/L		1		mmol/L
	mg/dL		0.2558		mmol/L
Protein	g/dL		10.0		g/L
Pyruvate	mg/dL		113.6		µmol/L
Sodium ion	mEq/L		1		mmol/L
Steroids					
17-hydroxycorticosteroids	mg/24 h		2.759		µmol/d
17-ketosteroids	mg/24 h		3.467		µmol/d
Testosterone	ng/mL		3.467		nmol/L
Theophylline	mg/L		5.550		µmol/L
Thyroid tests					
Thyroid-stimulating hormone	µU/mL		1		mU/L
Thyroxine (T_4)	µg/dL		12.87		nmol/L

Component	Present Unit	×	Conversion Factor	=	SI Unit
Thyroxine free	ng/dL		12.87		pmol/L
Triiodothyronine (T_3)	ng/dL		0.01536		nmol/L
Transferrin	mg/dL		0.01		g/L
Triglycerides	mg/dL		0.01129		mmol/L
Urea nitrogen	mg/dL		0.3570		mmol/L
Uric acid (urate)	mg/dL		59.48		µmol/L
Vitamin A (retinol)	µg/dL		0.03491		µmol/L
Vitamin B_{12}	pg/mL		0.7378		pmol/L
Vitamin C (ascorbic acid)	mg/dL		56.78		µmol/L
Vitamin D					
Cholecalciferol	µg/mL		2.599		nmol/L
25 OH-cholecalciferol	ng/mL		2.496		nmol/L
Vitamin E (alpha-tocopherol)	mg/dL		23.22		µmol/L
D-xylose	mg/dL		0.06661		mmol/L
Zinc	µg/dL		0.1530		µmol/L
Energy	kcal		4.1868		kj (kilojoule)
Blood pressure	mm Hg (= torr)		1.333		mbar

Source: Modified from Young D. S. (1987). Implementation of SI units for clinical laboratory data. Style specifications and conversion tables. *Annuls of Internal Medicine, 106, 114.*

APPENDIX C

Frequently Used Reference Values and Conversions



Note: Shading indicates the normal range where appropriate. To convert "old" to "new" units, multiply by the conversion factor at the foot of each column.

Source: Modified from Halliday, H. L., McClure, G., & Reid, M. (1985). *Handbook of neonatal intensive care* (2nd ed.). Philadelphia, PA: WB Saunders.

APPENDIX D

International Standards for Newborn Weight, Length, and Head Circumference by Gestational Age and Sex

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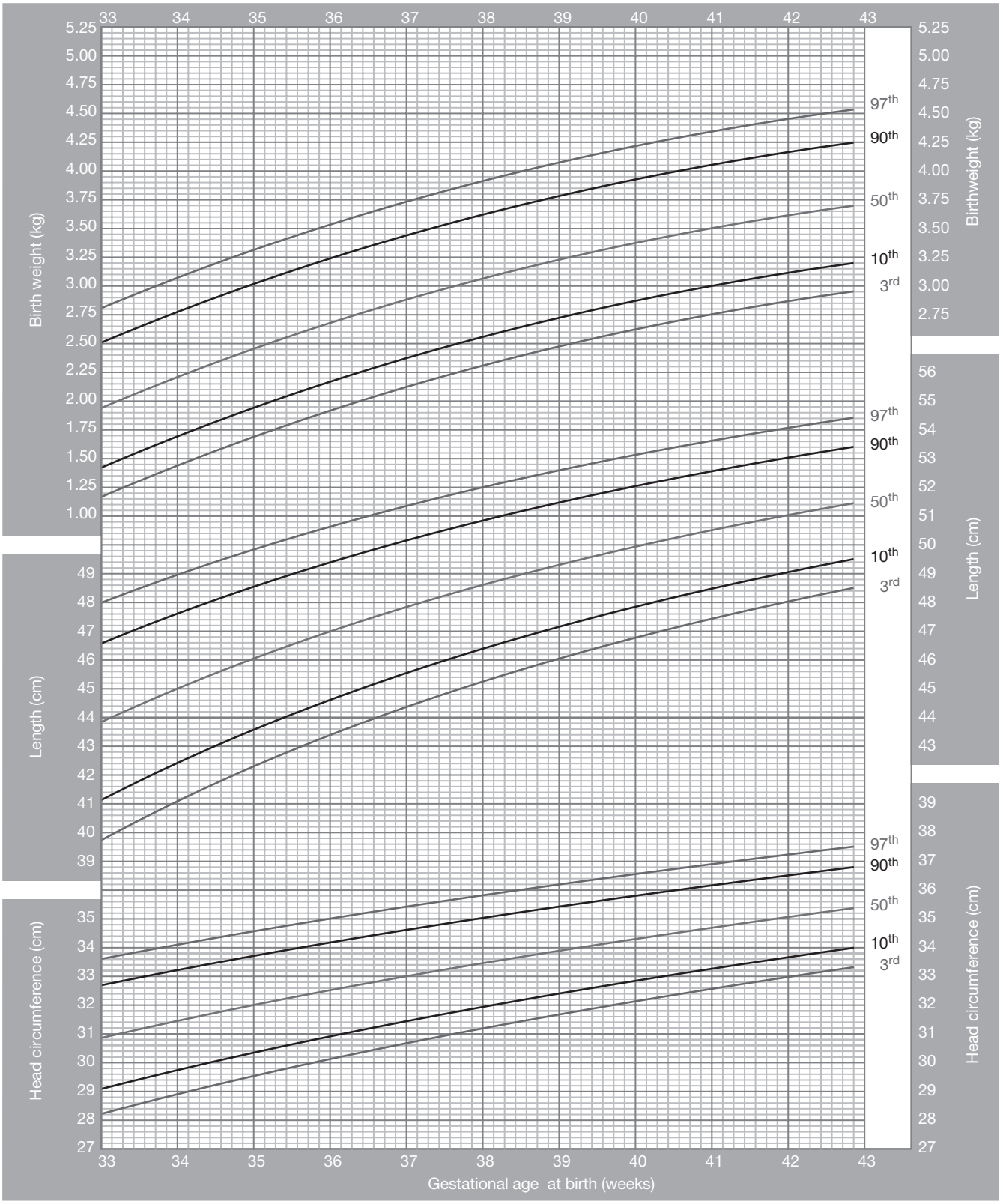
INTERGROWTH-21st

Boys



Source: INTERGROWTH-21st newborn size at birth standards. Reprinted by permission from Intergrowth-21st © 2009–2016. https://intergrowth21.tghn.org/articles/category/globalperinatal-package

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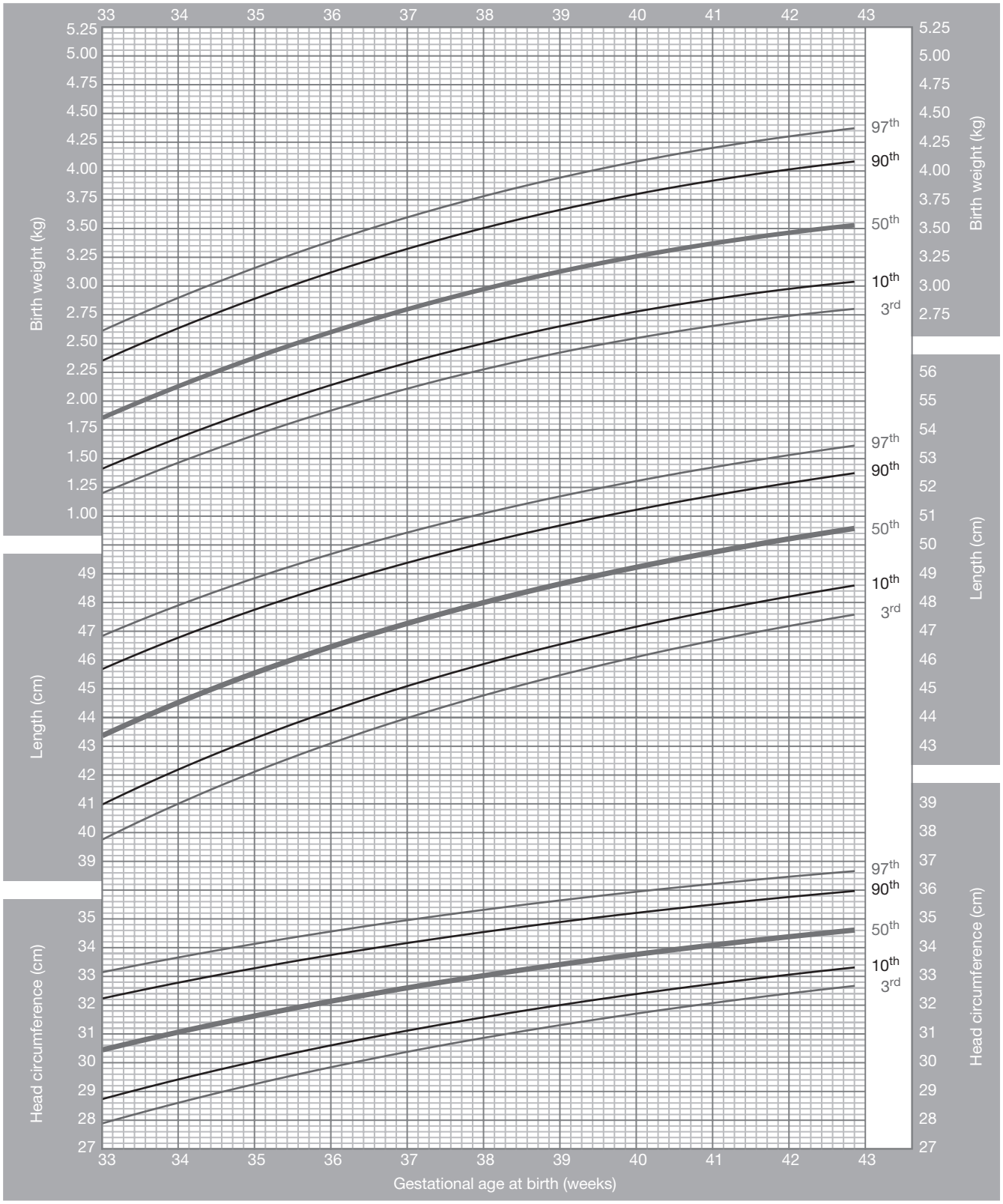
INTERGROWTH-21st

Girls



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